

34 **ABSTRACT**

35 **Background**

36 The lack of specific guidelines for seizure treatment after acute ischemic stroke
37 (AIS), makes the choice of an appropriate anti-seizure medication choice a challenge
38 for providers because each drug may have different adverse effects and outcomes.

39

40 **Methods**

41 In this retrospective matched cohort study, we analyzed a 20% sample of U.S.
42 Medicare beneficiaries aged 65 and over hospitalized for a first acute ischemic stroke
43 (AIS) between 2009-2021 who were discharged home. We included individuals who
44 were enrolled in Medicare hospital, medical and prescription drug insurance for 12
45 months prior to hospitalization and were not taking epilepsy-specific anti-seizure
46 medication (ESM) prior to hospitalization. We matched individuals on days from
47 discharge to ESM initiation. Individuals who initiated ESMs other than Levetiracetam,
48 i.e. Lamotrigine, Carbamazepine, Oxcarbazepine within 30 days of discharge (N = 229)
49 were matched to Levetiracetam initiators (N =687). We investigated the time to
50 seizure-like events, emergency department (ED) visits, and re-hospitalizations with a
51 follow-up of 180 days after initiation using a semi-competing risk framework. We
52 estimated the average treatment effect among the treated i.e. those who received
53 other ESMs.

54

55 **Results**

56 The matched cohort of 916 ESM initiators had a median age of 74 (IQR 69, 82)
57 and was 57% female and 71% Non-Hispanic White. Using the semi-competing risk

58 framework, those who received other ESM had a 37% lower hazard of seizure-like
59 events compared to receiving LEV, given that death had not occurred, hazard ratio
60 0.63 (95% CI: 0.43, 0.91). Among those who initiated ESMs other than Levetiracetam,
61 the hazard of ED visits and hospitalizations, given that death had not occurred, did not
62 differ significantly from initiating Levetiracetam; hazard ratios 1.00 (95% CI: 0.80,
63 1.25) and 0.98 (95% CI: 0.75, 1.28), respectively.

64

65 **Conclusion**

66 In a sample of Medicare beneficiaries hospitalized for acute ischemic stroke
67 and discharged home, initiating Levetiracetam in the outpatient setting was associated
68 with a higher risk of seizure-like events compared to other ESMs. However, no
69 significant differences were observed in the incidence of ED visits or hospitalizations,
70 suggesting comparable safety profiles in these broader clinical outcomes.

71 INTRODUCTION

72 Stroke is the most common cause of seizures in older adults.¹ Epilepsy-specific
73 anti-seizure medications (ESMs) are used for post-stroke seizure management.^{2,3}
74 Several ESM options are available, including Levetiracetam (LEV), Lamotrigine (LTG),
75 Valproate (VPA), Lacosamide (LAC), and others. Studies indicate that second-
76 generation ESMs, such as LEV and LTG, and third-generation options, including LAC,
77 are better tolerated in adults 65 and over compared to first-generation drugs like
78 phenytoin (PHT) and carbamazepine (CBZ).^{4,5} These newer classes of ESMs are
79 associated with fewer drug-drug interactions and adverse outcomes, making them
80 more suitable for older populations.

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

91 Among Medicare beneficiaries prescribed antiseizure medications, LEV is the
92 most commonly initiated drug for new-onset seizures and is often used as
93 monotherapy.^{11,12} Its popularity is largely attributed to its ease of administration
94 (available in both intravenous and tablet forms, with no titration required) and

95 minimal drug-drug interactions.^{13,14} These characteristics are particularly important
96 for elderly stroke survivors, who often have multiple comorbidities and are prescribed
97 anticoagulants, antiarrhythmics, or antihypertensive medications that may interact
98 with other ESMs.^{15,16}

99 While LEV's profile makes it a practical choice, known side effects such as
100 drowsiness and impaired balance can lead to falls, a critical concern in this
101 population.^{2,26} Falls often result in ED visits, hospitalizations, and loss of independence,
102 highlighting the heightened vulnerability of older ambulatory stroke survivors
103 discharged home - a less supervised yet highly at-risk group.¹⁷ Despite this, there is
104 limited evidence examining the impact of ESM choice on adverse outcomes such as
105 unsteadiness or seizure-like events in community-dwelling older stroke survivors. To
106 address these gaps, we investigated the relationship between outpatient ESM choice
107 within 30 days of stroke discharge and subsequent healthcare utilization and seizure-
108 like events in AIS survivors aged 65 and older discharged home.

109

110 **METHODS**

111 This study was approved by the Mass General Brigham Institutional Review
112 Board and followed the Strengthening the Reporting of Observational Studies in
113 Epidemiology (STROBE) reporting guidelines.¹⁸ The requirement for informed consent
114 was waived in our study as we performed a secondary analysis of data routinely
115 collected for billing. The data supporting this study's findings were collected by The
116 Centers for Medicare & Medicaid Services (CMS) and were made available by CMS
117 with no direct identifiers.¹⁹ All results were aggregated following CMS Cell Suppression
118 Policies. Restrictions apply to the availability of these data, which were used under

119 license for this study. Medicare data are available through CMS with their permission.

120 We included the code which produced the findings in the supplemental materials

121 (Supplementary materials – analytical code).

122

123 **Study Design**

124 We conducted a retrospective analysis of U.S. administrative claims data using
125 a matched cohort study design.²⁰ Our focus was on individuals over 65 years old, since
126 this population is more vulnerable to adverse outcomes because of its greater
127 frequency of multiple comorbidities.²¹ We analyzed a 20% sample of U.S. Medicare
128 health insurance beneficiaries, including only adults aged 65 and over discharged
129 home after a hospitalization for AIS between January 1, 2009, and September 30,
130 2021. Hospitalizations were selected from the Medicare Provider Analysis and Review
131 (MedPAR) database based on principal diagnosis codes for AIS. We selected
132 International Classification of Diseases, 9th Revision (ICD-9) codes 433, 434, 436, and
133 ICD-10 codes I63, a validated strategy to capture AIS in administrative databases.²²

134 We included Medicare beneficiaries who were enrolled in the traditional
135 Medicare Part A (hospital insurance), Part B (medical insurance), and Part D (drug
136 prescription coverage) continuously for 12 months before their admission for stroke.
137 We included first stroke admission, using at least 1 year of look back to identify prior
138 stroke.²³ We focused on outpatient medication initiation and outcomes in community-
139 dwelling stroke survivors. We included individuals who were discharged home and did
140 not include those who were discharged to a skilled nursing facility or other inpatient
141 facility.

142 We excluded Medicare beneficiaries with an ESM prescription in the 120-day
143 period before hospitalization, to remove prevalent ESM users. A 120-day look-back
144 period accounts for patients with prescriptions of 90-day supplies, as well as a 30-day
145 grace period in order to capture stockpiling of earlier medication refills. We focused on
146 ESM monotherapy, so patients prescribed more than one ESM were excluded.
147 Additional details on sample selection are included in Supplemental Material –
148 Supplemental Methods and Table S1.

149

150 **Participant Characteristics**

151 We described the following demographic characteristics for the sample: age,
152 sex, race and ethnicity. Reported race and ethnicity (Non-Hispanic White, Non-
153 Hispanic Black, Hispanic, Asian, Other) were categorized using the Research Triangle
154 Institute (RTI) race/ethnicity variable provided in Master Beneficiary Summary File
155 (MBSF).²⁴

156 We identified baseline comorbid conditions using Medicare’s Chronic Condition
157 Warehouse (CCW).²⁵ We considered a patient to have a condition at baseline if they
158 met the diagnosis definition prior to their stroke admission. In addition, we reported
159 the presence of a claim with an ICD code for arrhythmia (ICD-9 code 427.x and ICD-10
160 codes I48.x and I49.x) within the 12 months prior to admission, as certain ESMs are
161 less appropriate for individuals with specific types of arrhythmia (e.g., lacosamide and
162 its dose-dependent association with atrioventricular block and PR interval
163 prolongation).²⁶ We identified beneficiaries with baseline dementia using a validated
164 definition of AD/ADRD, which had excellent accuracy as demonstrated by a CV-AUC of
165 0.94.²⁷ The validated definition of dementia was developed using ICD-10 codes, so we

166 used a previously published crosswalk of ICD-10 to ICD-9 codes to identify beneficiaries
167 with dementia with ICD-9 claims (Supplemental Table S2).²⁸

168 Using claims data, we captured clinical factors that may influence ESM choice
169 and are associated with seizure outcomes and healthcare utilization: Stroke severity,
170 which correlates with higher modified Rankin Scores (mRS)²⁹, is a well-established risk
171 factor for late seizures.³⁰ Additionally, individuals with higher mRS scores at discharge
172 are more likely to have unfavorable outcomes, which may lead to ED visits and
173 hospitalizations. The mRS has seven total categories ranging from no or low disability
174 to death: 0 (no symptoms), 1 (no significant disability), 2 (slight disability), 3 (moderate
175 disability), 4 (moderate to severe disability), 5 (severe disability), 6 (death).^{31,32} For this
176 study, we used a validated claims-based algorithm to classify mRS as a binary outcome,
177 grouping scores of 0 to 3 and 4 to 6. The algorithm was able to accurately identify
178 disability status with an ROC AUC of 0.85.³³

179

180 **Matching Characteristics**

181 A common issue in real-world time-to-event analysis is immortal time bias due
182 to misaligned treatment start.³⁴ Our sample was selected on initiation of treatment
183 within 30 days of discharge, but healthcare utilization and outcomes may vary within
184 this window. To address this, we utilized a matched cohort design, matching initiators
185 in our comparison groups on days to initiation.³⁵

186 The ESM initiators were defined as the beneficiaries with therapy initiation
187 within 30 days of post-stroke discharge, beginning at the index acute hospitalization
188 discharge date. Prescription claims were identified in the Medicare Part D prescription
189 data using the generic and commercial brand names listed in Supplemental Table S3.

190 We used an intention-to-treat strategy, so we categorized individuals based on
191 whether they were prescribed a drug, indicated by a prescription claim for ESM.
192 We grouped ESM initiators into two groups for matching: LEV initiators and
193 other ESM Initiators, which includes LTG, LAC, CBZ, VPA and other ESMs. For each
194 beneficiary in use of other ESM, we identified 3 matches undergoing treatment with
195 LEV. We calculated the Mahalanobis distance from other ESM Initiators to LEV
196 initiators based on days from discharge to medication initiation and selected matches
197 based on the shortest distance.³⁶ In this matching process patients on LEV were used
198 as controls for each patient using another ESM (matching without replacement).

199

200 **Outcomes**

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

204 We measured the time to seizure-like events using claims with diagnosis codes
205 for seizure-like events from the inpatient, outpatient and carrier claims files. A list of
206 seizure diagnosis codes was identified from the CCW definition of epilepsy and is
207 included in Supplemental Table S4. We considered individuals to meet the definition
208 for a seizure-like event if they had one inpatient claim or two outpatient claims
209 occurring more than one day apart. We considered the time to the first day the
210 individual met the criteria.

211 We identified hospital readmissions using acute hospitalizations claims
212 occurring after the index stroke hospitalization in the MedPAR file. ED visits were

213 identified using outpatient and inpatient claims with revenue center code indicative of
214 an ED visits (0450, 0451, 0452, 0456, 0459, 0981).³⁷

215 We used the beneficiaries date of death [BENE_DEATH_DT] from the Medicare
216 MBSF, which comes from several sources including the Social Security Administration.
217 Overall 99% of the death information in the MBSF has been validated.³⁸

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

222

223 **Statistical Analysis**

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

227 We used a semi-competing risks framework to analyze time to seizure like
228 events, ED visits, and hospital readmission with mortality as a competing risk. The
229 semi-competing risks framework is described previously in Haneuse and Lee 2016.³⁹ In
230 brief, this framework allows us to consider the occurrence of a non-terminal event
231 (seizure like events, readmission, ED visit), which is subject to a terminal event (death).

232 We used an illness-death model, which defines 3 hazard functions. The first hazard
233 function is for seizure-like events, given that neither seizure-like events nor death has
234 occurred. The second hazard function is for death, given that neither seizure-like
235 events n nor death has occurred. The third function is for time to death after seizure
236 like event has occurred. Baseline hazard functions for all survival models were

237 structured using B-splines. We presented results for the illness-death model based on
238 the semi-Markov specification. We used the SemiCompRisk and SemiCompRiskFreq
239 package for R.

240 Models were adjusted for days to initiation, age, modified Rankin score, and
241 baseline depression. We did not have missing data for the covariates included in the
242 model. A table with covariates incrementally added to the model specification can be
243 found in the Supplemental Material. We adjusted for age and modified Rankin score as
244 these are related to the outcomes of interest, but did not meet the definition of
245 confounding because they were not related to the exposure. We used a 0.2 threshold
246 for defining a substantial difference based on standardized mean differences.

247

248 **Secondary Pre-planned Analysis**

249 We also repeated our analysis, stratifying by age less than or equal to 75 and
250 greater than 75. For this analysis, we did not include medications with fewer than 10
251 initiators.

252

253 **Sensitivity Analysis**

254 A potential concern is the misclassification of seizure-like events when using
255 claims data. To assess the extent to which our results might vary with different
256 definitions of the same construct, we conducted sensitivity analyses using alternative
257 methods to identify seizure-like events. First, we applied the standard CCW definition,
258 which requires one inpatient claim or two outpatient claims suggestive of epilepsy,
259 occurring on different dates. Second, we employed a more sensitive approach that
260 included any inpatient or outpatient claim for seizure-like events irrespective of date.

261 Third, we tested the inclusion of additional ICD codes for seizure-like events,
262 incorporating less specific codes for convulsions. These alternative definitions and
263 their impact on the results are detailed in Supplementary material (Table S5).

264

265 **RESULTS**

266 Descriptive statistics for the sample are provided in Table 1. The 229 other ESM
267 initiators were matched to 687 Levetiracetam initiators, for a total sample size of 916
268 individuals. The study sample was 57% female, had a median age of 74 years old
269 (interquartile range 69 to 81) and was 71% Non-Hispanic White. The percentage of
270 individuals with Alzheimer’s disease and related dementia (AD/ADRD) in the matched
271 sample was 8% for Other ESM and 4% for Levetiracetam initiators (SMD: 0.16).
272 Depression was present at baseline in 60% of Other ESM vs in 36% of Levetiracetam
273 initiators (SMD: 0.5). At discharge, 50% of Other ESM and to 42% of Levetiracetam
274 initiators had an mRS indicative of moderate to severe disability (SMD: 0.18). In the 12
275 months prior to admission, 34% of LEV and 38% of Other ESM initiators had a claim for
276 arrhythmia (SMD: 0.11).

277 Using a 0.2 threshold for defining a substantial difference based on
278 standardized mean differences, age was found to be significantly associated with drug
279 choice. Among individuals aged 65–69, 29% initiated Other ESMs compared with
280 32.3% of matched Levetiracetam initiators in the same age range.

281

282 **Association of ESM Choice and Outcomes**

283 In the matched sample of 916 individuals, there were 298 seizure-like events,
284 465 ED visits, 382 hospital re-admissions and 137 mortality events within a follow-up

285 period of 180 days. The average follow up time (to end of the follow-up window or
286 death) was 163 days and the total follow up time was 410 person-years. Cumulative
287 incidence curves for the outcomes are shown in Supplemental Materials – Figures 1-3.
288 We report the results from the adjusted multivariable models investigating the
289 association between ESM Choice and outcomes in Table 2-4. Survival curves for the
290 outcomes are shown in Supplemental Materials – Figures 4-6. Among those who
291 initiated ESMs other than Levetiracetam, the hazard of seizure-like events (given death
292 has not occurred) was 37% lower than if they had initiated Levetiracetam, hazard ratio
293 0.63 [95% CI, 0.43, 0.91] (Table 2). The hazard of ED visits and readmission, given death
294 had not occurred, was not different for the other ESM group compared with receiving
295 LEV, with hazard ratios of 1.00 (95% CI: 0.80, 1.25) for ED visits and 0.98 (95% CI: 0.75,
296 1.28) for hospital readmission (Table 3 & 4).

297

298 **Results of Secondary Pre-planned Analysis**

299 In our analysis stratified by age, the hazard ratio for seizure-like events, given
300 that death had not occurred was 0.54 (95% CI: 0.28, 1.04) for those less than or equal
301 to 75 and 0.68 (95% CI: 0.45, 1.01) for individuals over 75 (Table 5). The results of the
302 sensitivity analysis did not alter our conclusions (Supplemental Table S5 and S6).

303

304 **DISCUSSION**

305 In a sample of Medicare beneficiaries hospitalized for acute ischemic stroke, we
306 compared outcomes for matched individuals initiated on different ESMs. We found the
307 risk of seizure-like events in those who initiated on Levetiracetam greater compared
308 with other medications. In the context of insufficient guidance for seizure treatment in

309 older patients, our study brings important information on post-stroke seizure control
310 and ESM choice in this population.

311 We identified several previous randomized controlled studies on ESM choice for
312 treatment of post-stroke seizures and epilepsy that are relevant to our study. Gilad et
313 al. 2007 compared LTG (N = 32) with controlled-release carbamazepine (CR-CBZ)
314 (N=32) and Consoli et a. 2012 compared LEV (n=52) with CR-CBZ (N = 54).^{40,41} A
315 detailed review of these studies has been previously published by Brigo et al. 2018.⁴ In
316 both previous studies of ESM choice, no difference was found in seizure freedom
317 between groups, but both studies had a small number of patients included and thus
318 may have been underpowered. In addition, randomized controlled trials are restrictive
319 in their enrollment criteria and may have selection bias due to withdrawal from the
320 trial. The average age of participants in Gilad et al. 2007 was 67.2 (SD 2.4) for LTG and
321 67.7 (SD 2.6) compared with our study population which had a median age of 74 (IQR
322 69 to 81) and participants ranging from 65 years old to over 85 years old. In Gilad et al.
323 2007, 3% of participants taking LTG and 31% of CR_CBZ withdrew from the trial due to
324 adverse effects. Our study showed lower hazard of seizure-like events for other ESM
325 initiators compared to receiving LEV.

326 We identified a population-based registry study on ESM choice in post-stroke
327 epilepsy. Winter et al. 2022 followed 216 patients initiated on ESM monotherapy (LEV,
328 LTG, LAC, VPA and eslicarbazepine (ESL)) for 12 months.⁷ The study reported lower
329 seizure frequency in ESMs with selectivity to the slow-inactivated state of sodium
330 channels (LAC, ESL) compared with other mechanisms of action.

331 Monotherapy with LEV has been previously found to have an effectiveness of more
332 than 80% in preventing seizures.⁴² Unlike our study, other smaller studies did not find

333 statistically significant differences in seizure-like events between post-stroke patients
334 treated with LEV compared with other ESMs.⁴¹ These findings highlight the necessity of
335 future guidelines for ESM therapy to distinguish older populations, considering the
336 impact of increased seizure relapse in this group with an existing high risk of deficits
337 and adverse outcomes.⁴³ Moreover, previous randomized controlled studies present
338 comparisons of ESM versus placebo, which does not help in drug type choice and can
339 result in seizure relapse outcomes, as presented in our results.^{44,45,46}

340 Stroke patients have a high risk of hospital readmission.⁴⁷⁻⁴⁹ A previous study
341 found a total of more than 30% of stroke survivors being readmitted.⁴⁸ The presence of
342 a seizure diagnosis in this population has been reported as a contributing factor to
343 both new hospitalizations and mortality risk.^{47,49} We did not identify any studies on
344 ESM choice and differences in healthcare utilization (ED Visits and readmission). In our
345 cohort, there was no difference in the ED visits, hospitalizations between patients
346 treated with Levetiracetam compared to Other ESM.

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

355

356 **Limitations**

357 The findings for our population sample might not be generalizable to groups not
358 included in this study such as Medicare beneficiaries enrolled in Part C (Medicare
359 Advantage), or patients not enrolled in Medicare prescription drug plans (Part D).
360 Lastly, our sample of dementia patients initiated on other ESM was too small to
361 complete stratification as initially planned.

362 This study excluded beneficiaries discharged to inpatient rehabilitation units or
363 SNFs. Patients are discharged to these facilities usually present with variable
364 disabilities and would benefit from assessment in future studies.⁵⁰ We also focused on
365 subacute outcomes of ESM treatment on acute ischemic stroke patients. Later studies
366 could explore chronic outcomes, especially when considering the different patterns of
367 ESM use and adverse effects among this population.⁹

368 Due to existing limitations in the dataset, some residual confounding factors could
369 not be controlled. We were not able to adjust for factors associated with stroke
370 severity and seizure outcomes, such as stroke territory. We found that as covariates
371 were added incrementally to the model specification, the differences between
372 treatment groups became larger, as indicated by lower hazard ratios (Table S6).
373 Additional variables, could reduce variance and improve precision, but would not
374 necessarily enhance the validity of the model because of their strong correlation with
375 variables already included the model. After the adjustments made, residual
376 confounding from unmeasured factors is likely minimal.

377 While the use of claims-based data is reliable, it also has limitations such as missing
378 data and a lack of granular seizure outcome data. Data are also absent on seizure
379 frequency, seizure type, date of last seizure episode, or indication for ESM treatment.
380 We tried to address this last point by selecting ESMs to include in this study that are

381 primarily indicated for treatment of seizures. Lastly, certain ESM presented with too
382 small groups and so we did not have the power to see small differences between
383 groups.

384

385 **ACKNOWLEDGEMENTS**

386 **Funding**

387 This study was supported by the NIH (1R01AG073410-01)

388

389 **Disclosures**

390 J.D.B. completed the data analysis, drafted and edited the. R.C.M. drafted, edited, and
391 revised the manuscript. S.S. and M.S. were involved with study design and statistical
392 analysis. B.W. and L.S. were involved in the study conceptualization and revised the
393 manuscript. J.P.N. facilitated data access and revised the manuscript. S.H. was involved
394 in study design, supervising the study development, and revising the manuscript.

395 L.M.V.R.M. was involved in study design and conceptualization, obtaining data access,
396 and supervising the study development and revising the manuscript.

397

398 **SOURCES OF FUNDING**

399 This study was supported by the NIH (1R01AG073410-01)

400

401 **DISCLOSURES**

402 J.D.B., R.C.M.,S.S., M.S., L.M.S., J.P.N., S.H., and M.B.W. have no conflict of interest to
403 disclose. M.B.W. is a co-founder, scientific advisor, consultant to, and has personal
404 equity interest in Beacon Biosignals. L.M.V.R.M. receives research support from the

405 Epilepsy Foundation of America, the National Institute of Neurological Disorders and
406 Stroke, and the National Institute on Aging and reports no conflict of interest.

407

408

409 REFERENCES

410

- 411 1. Galovic M, Ferreira-Atuesta C, Abraira L, et al. Seizures and Epilepsy After
412 Stroke: Epidemiology, Biomarkers and Management. *Drugs Aging*. 2021;38(4):285-299.
413 doi:10.1007/s40266-021-00837-7
- 414 2. Brodie MJ, Elder AT, Kwan P. Epilepsy in later life. *The Lancet Neurology*.
415 2009;8(11):1019-1030. doi:10.1016/S1474-4422(09)70240-6
- 416 3. Winstein CJ, Stein J, Arena R, et al. Guidelines for Adult Stroke Rehabilitation
417 and Recovery: A Guideline for Healthcare Professionals From the American Heart
418 Association/American Stroke Association. *Stroke*. 2016;47(6).
419 doi:10.1161/STR.0000000000000098
- 420 4. Brigo F, Lattanzi S, Zelano J, et al. Randomized controlled trials of antiepileptic
421 drugs for the treatment of post-stroke seizures: A systematic review with network
422 meta-analysis. *Seizure*. 2018;61:57-62. doi:10.1016/j.seizure.2018.08.001
- 423 5. Lattanzi S, Trinka E, Del Giovane C, Nardone R, Silvestrini M, Brigo F.
424 Antiepileptic drug monotherapy for epilepsy in the elderly: A systematic review and
425 network meta-analysis. *Epilepsia*. 2019;60(11):2245-2254. doi:10.1111/epi.16366
- 426 6. Holtkamp M, Beghi E, Benninger F, et al. European Stroke Organisation
427 guidelines for the management of post-stroke seizures and epilepsy. *European Stroke*
428 *Journal*. 2017;2(2):103-115. doi:10.1177/2396987317705536
- 429 7. Winter Y, Uphaus T, Sandner K, Klimpe S, Stuckrad-Barre S von, Groppa S.
430 Efficacy and safety of antiseizure medication in post-stroke epilepsy. *Seizure*.
431 2022;100:109-114. doi:10.1016/j.seizure.2022.07.003
- 432 8. Moura LMVR, Smith JR, Yan Z, et al. Patterns of anticonvulsant use and adverse
433 drug events in older adults. *Pharmacoepidemiol Drug Saf*. 2021;30(1):28-36.
434 doi:10.1002/pds.5139
- 435 9. By the 2023 American Geriatrics Society Beers Criteria® Update Expert Panel.
436 American Geriatrics Society 2023 updated AGS Beers Criteria® for potentially
437 inappropriate medication use in older adults. *J American Geriatrics Society*.
438 2023;71(7):2052-2081. doi:10.1111/jgs.18372
- 439 10. Tsao CW, Aday AW, Almarzooq ZI, et al. Heart Disease and Stroke Statistics—
440 2023 Update: A Report From the American Heart Association. *Circulation*. 2023;147(8).
441 doi:10.1161/CIR.0000000000001123
- 442 11. Terman SW, Youngerman BE, Choi H, Burke JF. Antiseizure medication
443 treatment pathways for US Medicare beneficiaries with newly treated epilepsy.
444 *Epilepsia*. 2022;63(6):1571-1579. doi:10.1111/epi.17226
- 445 12. Practice guideline update summary: Efficacy and tolerability of the new
446 antiepileptic drugs I: Treatment of new-onset epilepsy | Neurology. Accessed
447 December 9, 2024. <https://www.neurology.org/doi/10.1212/WNL.0000000000005755>

- 448 13. Fiani B, Andraos C, Mabry I, Siddiqi J. A Comparison of Seizure Prophylaxis:
449 Phenytoin Versus Levetiracetam. *Cureus*. Published online May 11, 2021.
450 doi:10.7759/cureus.14956
- 451 14. Fang T, Valdes E, Frontera JA. Levetiracetam for Seizure Prophylaxis in
452 Neurocritical Care: A Systematic Review and Meta-analysis. *Neurocrit Care*.
453 2022;36(1):248-258. doi:10.1007/s12028-021-01296-z
- 454 15. Goldstein R, Jacobs AR, Zighan L, Gronich N, Bialer M, Muszkat M. Interactions
455 Between Direct Oral Anticoagulants (DOACs) and Antiseizure Medications: Potential
456 Implications on DOAC Treatment. *CNS Drugs*. 2023;37(3):203-214.
457 doi:10.1007/s40263-023-00990-0
- 458 16. Patsalos PN, Perucca E. Clinically important drug interactions in epilepsy:
459 interactions between antiepileptic drugs and other drugs. *The Lancet Neurology*.
460 2003;2(8):473-481. doi:10.1016/S1474-4422(03)00483-6
- 461 17. Pohl P, Nordin E, Lundquist A, Bergström U, Lundin-Olsson L. Community-
462 dwelling older people with an injurious fall are likely to sustain new injurious falls
463 within 5 years - a prospective long-term follow-up study. *BMC Geriatr*. 2014;14(1):120.
464 doi:10.1186/1471-2318-14-120
- 465 18. Von Elm E, Altman DG, Egger M, et al. The Strengthening the Reporting of
466 Observational Studies in Epidemiology (STROBE) Statement: Guidelines for Reporting
467 Observational Studies. *Ann Intern Med*. 2007;147(8):573. doi:10.7326/0003-4819-147-
468 8-200710160-00010
- 469 19. Centers for Medicare and Medicaid Services. Centers for Medicare and
470 Medicaid Services. Accessed January 7, 2025. <https://www.cms.gov>
- 471 20. Fisher DP, Johnson E, Haneuse S, et al. Association Between Bariatric Surgery
472 and Macrovascular Disease Outcomes in Patients With Type 2 Diabetes and Severe
473 Obesity. *JAMA*. 2018;320(15):1570. doi:10.1001/jama.2018.14619
- 474 21. Lezaic N, Gore G, Josephson CB, Wiebe S, Jetté N, Keezer MR. The medical
475 treatment of epilepsy in the elderly: A systematic review and meta-analysis. *Epilepsia*.
476 2019;60(7):1325-1340. doi:10.1111/epi.16068
- 477 22. McCormick N, Bhole V, Lacaille D, Avina-Zubieta JA. Validity of Diagnostic Codes
478 for Acute Stroke in Administrative Databases: A Systematic Review. Quinn TJ, ed. *PLoS*
479 *ONE*. 2015;10(8):e0135834. doi:10.1371/journal.pone.0135834
- 480 23. Moura LMVR, Donahue MA, Yan Z, et al. Comparative Effectiveness and Safety
481 of Seizure Prophylaxis Among Adults After Acute Ischemic Stroke. *Stroke*.
482 2023;54(2):527-536. doi:10.1161/STROKEAHA.122.039946
- 483 24. Eicheldinger C, Bonito A. More accurate racial and ethnic codes for Medicare
484 administrative data. *Health Care Financ Rev*. 2008;29(3):27-42.
- 485 25. Chronic Conditions Data Warehouse. Chronic Conditions Data Warehouse. July
486 1, 2025. Accessed January 7, 2025. <https://www2.ccwdata.org/web/guest/home/>
- 487 26. Yadav R, Schrem E, Yadav V, Jayarangaiah A, Das S, Theetha Kariyanna P.
488 Lacosamide-Related Arrhythmias: A Systematic Analysis and Review of the Literature.
489 *Cureus*. 13(12):e20736. doi:10.7759/cureus.20736
- 490 27. Moura LMVR, Festa N, Price M, et al. Identifying Medicare beneficiaries with
491 dementia. *J Am Geriatr Soc*. 2021;69(8):2240-2251. doi:10.1111/jgs.17183
- 492 28. ICD-9-CM to and from ICD-10-CM and ICD-10-PCS Crosswalk or General
493 Equivalence Mappings. National Bureau Of Economic Research. 2025.

- 494 <https://www.nber.org/research/data/icd-9-cm-and-icd-10-cm-and-icd-10-pcs->
495 [crosswalk-or-general-equivalence-mappings](https://www.nber.org/research/data/icd-9-cm-and-icd-10-cm-and-icd-10-pcs-crosswalk-or-general-equivalence-mappings)
- 496 29. Banks JL, Marotta CA. Outcomes Validity and Reliability of the Modified Rankin
497 Scale: Implications for Stroke Clinical Trials. *Stroke*. 2007;38(3):1091-1096.
498 doi:10.1161/01.STR.0000258355.23810.c6
- 499 30. Zöllner JP, Schmitt FC, Rosenow F, et al. Seizures and epilepsy in patients with
500 ischaemic stroke. *Neurol Res Pract*. 2021;3:63. doi:10.1186/s42466-021-00161-w
- 501 31. Rankin J. Cerebral Vascular Accidents in Patients over the Age of 60: II.
502 Prognosis. *Scott Med J*. 1957;2(5):200-215. doi:10.1177/003693305700200504
- 503 32. De Haan R, Limburg M, Bossuyt P, Van Der Meulen J, Aaronson N. The Clinical
504 Meaning of Rankin 'Handicap' Grades After Stroke. *Stroke*. 1995;26(11):2027-2030.
505 doi:10.1161/01.STR.26.11.2027
- 506 33. Habib M, Cazé De Medeiros R, Muhammad Ahsan S, et al. A Claims-Based
507 Machine Learning Classifier of Modified Rankin Scale in Acute Ischemic Stroke.
508 Published online February 11, 2025. doi:10.1101/2025.02.06.25321827
- 509 34. Grubic N, Johnston A, Randhawa VK, Humphries KH, Rosella LC, Maximova K.
510 Breaking Down Bias: A Methodological Primer on Identifying, Evaluating, and
511 Mitigating Bias in Cardiovascular Research. *Canadian Journal of Cardiology*. Published
512 online December 2024:S0828282X24013199. doi:10.1016/j.cjca.2024.12.022
- 513 35. Fisher DP, Johnson E, Haneuse S, et al. Association Between Bariatric Surgery
514 and Macrovascular Disease Outcomes in Patients With Type 2 Diabetes and Severe
515 Obesity. *JAMA*. 2018;320(15):1570. doi:10.1001/jama.2018.14619
- 516 36. Mahalanobis PC. On the Generalized Distance in Statistics. *Sankhyā: The Indian*
517 *Journal of Statistics*. 2008;80. <https://www.jstor.org/stable/48723335>
- 518 37. How to Identify Hospital Claims for Emergency Room Visits in the Medicare
519 Claims Data | ResDAC. Accessed December 9, 2024. [https://resdac.org/articles/how-](https://resdac.org/articles/how-identify-hospital-claims-emergency-room-visits-medicare-claims-data)
520 [identify-hospital-claims-emergency-room-visits-medicare-claims-data](https://resdac.org/articles/how-identify-hospital-claims-emergency-room-visits-medicare-claims-data)
- 521 38. Death Information in the Research Identifiable Medicare Data | ResDAC.
522 Accessed April 19, 2024. [https://resdac.org/articles/death-information-research-](https://resdac.org/articles/death-information-research-identifiable-medicare-data)
523 [identifiable-medicare-data](https://resdac.org/articles/death-information-research-identifiable-medicare-data)
- 524 39. Haneuse S, Lee KH. Semi-Competing Risks Data Analysis: Accounting for Death
525 as a Competing Risk When the Outcome of Interest is Non-Terminal. *Circ Cardiovasc*
526 *Qual Outcomes*. 2016;9(3):322-331. doi:10.1161/CIRCOUTCOMES.115.001841
- 527 40. Gilad R, Sadeh M, Rapoport A, Dabby R, Boaz M, Lampl Y. Monotherapy of
528 Lamotrigine Versus Carbamazepine in Patients With Poststroke Seizure. *Clinical*
529 *Neuropharmacology*. 2007;30(4):189. doi:10.1097/WNF.0b013e3180333069
- 530 41. Consoli D, Bosco D, Postorino P, et al. Levetiracetam versus carbamazepine in
531 patients with late poststroke seizures: a multicenter prospective randomized open-
532 label study (EpIC Project). *Cerebrovasc Dis*. 2012;34(4):282-289.
533 doi:10.1159/000342669
- 534 42. Kutlu G, Gomceli YB, Unal Y, Inan LE. Levetiracetam monotherapy for late
535 poststroke seizures in the elderly. *Epilepsy Behav*. 2008;13(3):542-544.
536 doi:10.1016/j.yebeh.2008.04.025
- 537 43. Perucca E, Berlowitz D, Birnbaum A, et al. Pharmacological and clinical aspects
538 of antiepileptic drug use in the elderly. *Epilepsy Research*. 2006;68:49-63.
539 doi:10.1016/j.eplepsyres.2005.07.017

- 540 44. Peter-Derex L, Philippeau F, Garnier P, et al. Safety and efficacy of prophylactic
541 levetiracetam for prevention of epileptic seizures in the acute phase of intracerebral
542 haemorrhage (PEACH): a randomised, double-blind, placebo-controlled, phase 3 trial.
543 *The Lancet Neurology*. 2022;21(9):781-791. doi:10.1016/S1474-4422(22)00235-6
544 45. Manreza MLG de, Pan TA, Carbone EQ, et al. Efficacy and safety of
545 levetiracetam as adjunctive therapy for refractory focal epilepsy. *Arq Neuropsiquiatr*.
546 2021;79(4):290-298. doi:10.1590/0004-282X-ANP-2020-0082
547 46. Wu T, Lim SN, Tsai JJ, et al. A randomized, double-blind, double-dummy,
548 multicenter trial comparing the efficacy and safety of extended- and immediate-
549 release levetiracetam in people with partial epilepsy. *Seizure*. 2018;62:84-90.
550 doi:10.1016/j.seizure.2018.09.008
551 47. Kuohn LR, Herman AL, Soto AL, et al. Hospital Revisits for Post-Ischemic Stroke
552 Epilepsy after Acute Stroke Interventions. *Journal of Stroke and Cerebrovascular*
553 *Diseases*. 2022;31(1):106155. doi:10.1016/j.jstrokecerebrovasdis.2021.106155
554 48. Readmission after stroke in a hospital-based registry | *Neurology*. Accessed
555 December 2, 2024. <https://www.neurology.org/doi/10.1212/WNL.0b013e31820a0cd8>
556 49. Lekoubou A, Bishu KG, Ovbiagele B. Influence of a Comorbid Diagnosis of
557 Seizure on 30-Day Readmission Rates Following Hospitalization for an Index Stroke.
558 *Journal of Stroke and Cerebrovascular Diseases*. 2020;29(2):104479.
559 doi:10.1016/j.jstrokecerebrovasdis.2019.104479
560 50. Broderick JP, Abir M. Transitions of Care for Stroke Patients: Opportunities to
561 Improve Outcomes. *Circ: Cardiovascular Quality and Outcomes*. 2015;8(6_suppl_3).
562 doi:10.1161/CIRCOUTCOMES.115.002288
563
564

565

566 **FIGURES LEGENDS**

567

568 **Figure 1. Sample Inclusion Criteria**

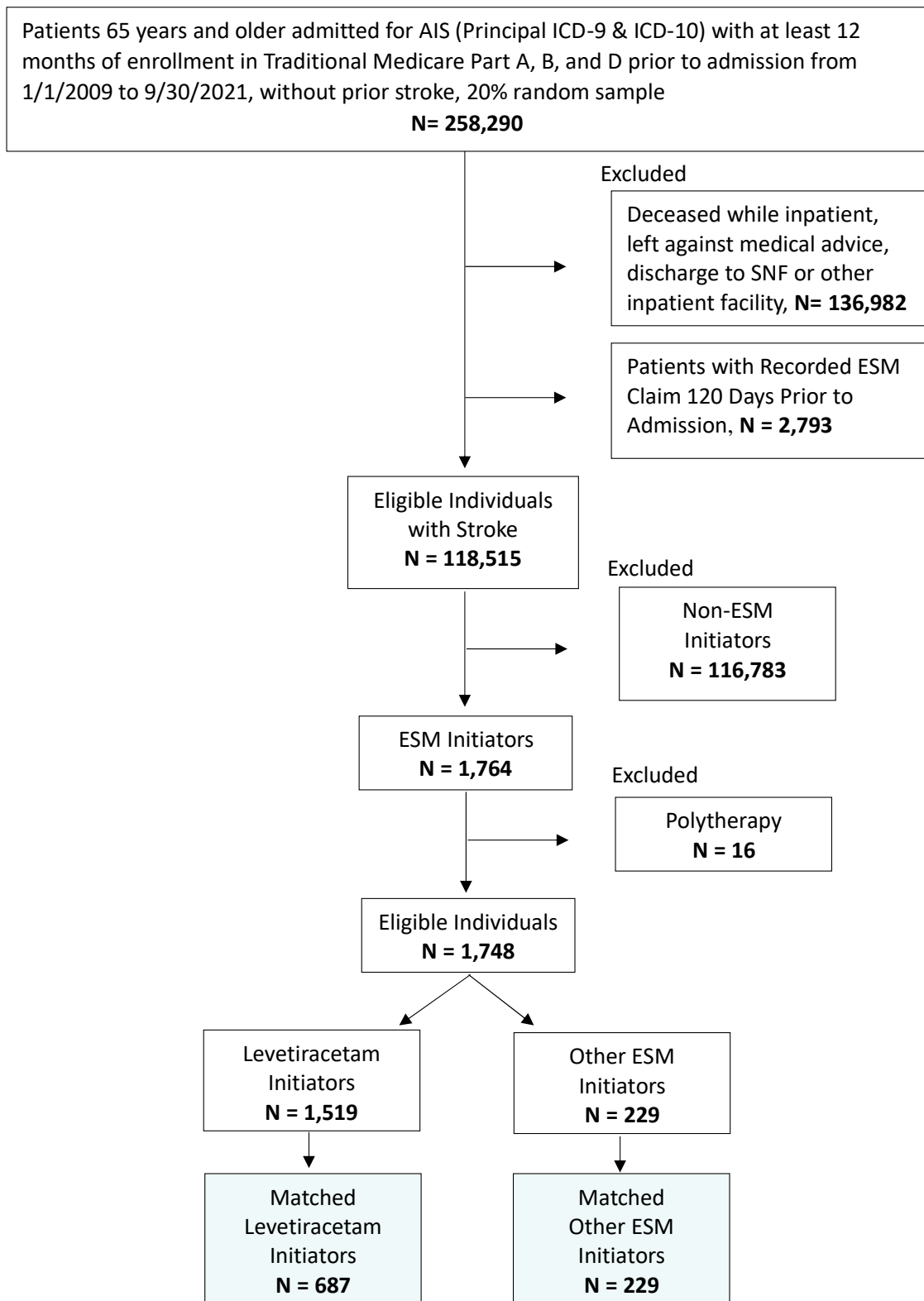
569 AIS, Acute Ischemic Stroke; SNF Skilled Nursing Facility; ESM Epilepsy-Specific Anti-

570 Seizure Medication

571

572

573 **FIGURES**



574
575
576
577
578

Figure 1. Sample Inclusion Criteria

AIS, Acute Ischemic Stroke; SNF Skilled Nursing Facility; ESM Epilepsy-Specific Anti-Seizure Medication

579 **TABLES**

580

581 Table 1. Sample Characteristics

Variable		Overall	Matched	Other ESM	SMD
		N = 916	Levetiracetam Initiator N = 687	Initiator N = 229	
Age	65-69	266 (29.0)	222 (32.3)	44 (19.2)	0.37
	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)	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)	0.17
	Black or African American	126 (13.8)	95 (13.8)	31 (13.5)	
	Hispanic	98 (10.7)	***	***	
	Other/Unknown	40 (4.4)	***	***	
Length of hospital Stay	1 to 5 days	710 (77.5)	538 (78.3)	172 (75.1)	0.13
	6 to 10 days	139 (15.2)	105 (15.3)	34 (14.8)	
	10+ days	67 (7.3)	44 (6.4)	23 (10.0)	
Modified Rankin Score	0 (No disability)	519 (56.7)	404 (58.9)	115 (50.2)	0.18
	1 (Disability)	396 (43.3)	282 (41.1)	114 (49.8)	
Dementia	Yes	49 (5.3)	30 (4.4)	19 (8.3)	0.16
	No	867 (94.7)	657 (95.6)	210 (91.7)	
Arrhythmia	Yes	315 (34.4)	227 (33.0)	88 (38.4)	0.11
	No	601 (65.6)	460 (67.0)	141 (61.6)	
Acute MI		83 (9.1)	67 (9.8)	16 (7.0)	0.10
Atrial Fibrillation		211 (23.0)	153 (22.3)	58 (25.3)	0.07
Cataract		571 (62.3)	403 (58.7)	168 (73.4)	0.31
Chronic Kidney		415 (45.3)	302 (44.0)	113 (49.3)	0.11

COPD	330 (36.0)	235 (34.2)	95 (41.5)	0.15
CHF	355 (38.8)	246 (35.8)	109 (47.6)	0.24
Diabetes	492 (53.7)	354 (51.5)	138 (60.3)	0.18
Ischemic Heart Disease	597 (65.2)	433 (63.0)	164 (71.6)	0.18
Depression	383 (41.8)	246 (35.8)	137 (59.8)	0.50
Osteoporosis	176 (19.2)	123 (17.9)	53 (23.1)	0.13
Rheumatoid Arthritis/ Osteoarthritis	536 (58.5)	383 (55.7)	153 (66.8)	0.23
Asthma	169 (18.4)	121 (17.6)	48 (21.0)	0.09
Hyperlipidemia	784 (85.6)	580 (84.4)	204 (89.1)	0.14
Hypertension	842 (91.9)	623 (90.7)	219 (95.6)	0.20
Hypothyroidism	266 (29.0)	184 (26.8)	82 (35.8)	0.20

582 **Legend:** ESM, Epilepsy-Specific Anti-Seizure Medication; SMD, Standardized Mean
583 Difference; COPD, Chronic Obstructive Pulmonary Disease; CHF, Congestive Heart
584 Failure; MI, Myocardial Infarction. *** Small counts are censored in accordance with
585 Center for Medicare and Medicaid Cell Suppression Policy
586

587 Table 2. Hazard Ratios for Seizure-Like Events

Variable	Seizure-like Event	Death prior to Seizure-like Event	Death post Seizure-like Event
ESM treatment Group	0.63 (0.43, 0.91)	0.64 (0.37, 1.11)	1.02 (0.46, 2.24)
Days to Initiation	1.00 (0.98, 1.01)	1.00 (0.98, 1.03)	1.02 (0.98, 1.05)
Age (standardized at age 80, 10 year bins)	0.88 (0.72, 1.08)	1.14 (0.86, 1.51)	1.19 (0.81, 1.77)
Modified Rankin score	1.38 (0.95, 1.99)	2.82 (1.68, 4.73)	2.35 (1.19, 4.64)
Baseline Depression	1.26 (0.94, 1.69)	1.24 (0.79, 1.95)	1.12 (0.58, 2.15)

588

589 **Legend:** Hazard Ratios for Seizure-like Events with a follow up period of 180-Days after
590 medication initiation. Hazard ratios were calculated using a semi-competing risk
591 framework, with death as a competing risk. Hazard ratios were adjusted for age,
592 modified Rankin Score, baseline depression, and days from discharge to medication
593 initiation.

594

595 Table 3. Hazard Ratios for Emergency Department (ED) Visits

Variable	ED Visit	Death prior to ED Visit	Death post ED Visit
ESM treatment Group	1.00 (0.80, 1.25)	0.83 (0.44, 1.55)	0.74 (0.43, 1.27)
Days to Initiation	1.00 (0.99, 1.01)	0.98 (0.95, 1.01)	1.02 (1.00, 1.04)
Age (standardized at age 80, 10 year bins)	1.02 (0.90, 1.17)	1.34 (0.98, 1.85)	1.04 (0.79, 1.38)
Modified Rankin score	1.47 (1.16, 1.87)	2.77 (1.51, 5.07)	1.80 (1.11, 2.94)
Baseline Depression	1.22 (0.99, 1.49)	1.20 (0.70, 2.06)	1.06 (0.67, 1.66)

596

597 **Legend:** Hazard Ratios for ED Visits with a follow up period of 180-Days after
598 medication initiation. Hazard ratios were calculated using a semi-competing risk
599 framework, with death as a competing risk. Hazard ratios were adjusted for age,
600 modified Rankin Score, baseline depression, and days from discharge to medication
601 initiation.

602

603 Table 4. Hazard Ratios for Hospital Readmissions

Variable	Readmission	Death prior to Readmission	Death post Readmission
ESM treatment Group	0.98 (0.75, 1.28)	0.84 (0.43, 1.63)	0.69 (0.40, 1.19)
Days to Initiation	1.01 (0.99, 1.02)	0.97 (0.94, 1.01)	1.02 (0.99, 1.04)
Age (standardized at age 80, 10 year bins)	0.96 (0.82, 1.12)	1.42 (1.01, 1.99)	1.04 (0.79, 1.37)
Modified Rankin score	1.64 (1.22, 2.19)	3.98 (1.96, 8.06)	1.48 (0.91, 2.40)
Baseline Depression	1.12 (0.89, 1.40)	1.14 (0.64, 2.05)	1.14 (0.73, 1.78)

604

605 **Legend:** Hazard Ratios for Hospital Readmissions with a follow up period of 180-Days
606 after medication initiation. Hazard ratios were calculated using a semi-competing risk

607 framework, with death as a competing risk. Hazard ratios were adjusted for age,
608 modified Rankin Score, baseline depression, and days from discharge to medication
609 initiation.

610

611 Table 5. Hazard Ratios for Seizure-like Events, ED Visits, and Readmission, Stratified by
612 Age Group

613

Variable	Seizure	ED Visit	Readmission
Less than or equal to 75	0.54 (0.28, 1.04)	0.86 (0.57, 1.30)	1.05 (0.70, 1.58)
Over 75	0.68 (0.45, 1.01)	1.09 (0.82, 1.45)	0.98 (0.68, 1.39)

614

615 **Legend:** Hazard Ratios for outcomes, given that death did not occur, with a follow up
616 period of 180-Days after medication initiation. Hazard ratios were calculated using a
617 semi-competing risk framework, with death as a competing risk. Models were adjusted
618 for age, modified Rankin Score, baseline depression, and days from discharge to
619 medication initiation.

620

621

622