1   **Choice of Epilepsy Anti-Seizure Medications and Associated Outcomes in Medicare**
2   **Beneficiaries**
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ABSTRACT

Background

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

Methods

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

Results

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

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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   different 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.

3

INTRODUCTION

Stroke is the most common cause of seizures in older adults.[1] Epilepsy-specific anti-seizure medications (ESMs) are used for post-stroke 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 65 and over compared to first-generation drugs like phenytoin (PHT) 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 comparative 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 Medicare beneficiaries 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

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

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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.

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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

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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

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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

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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**

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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

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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

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.

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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.

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FIGURES LEGENDS

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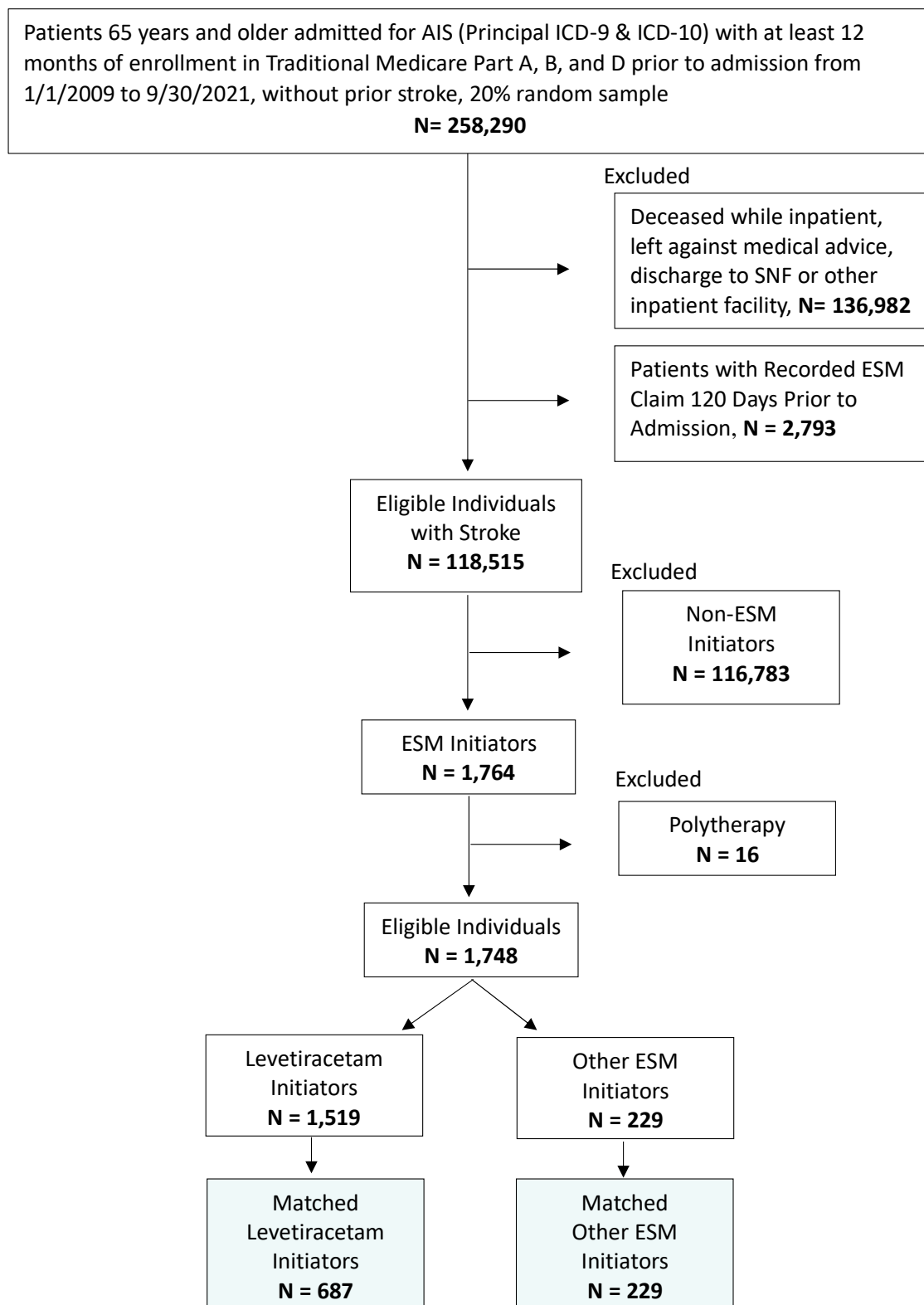**Figure 1. Sample Inclusion Criteria**

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

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573 **FIGURES**

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576 **Figure 1. Sample Inclusion Criteria**
577 AIS, Acute Ischemic Stroke; SNF Skilled Nursing Facility; ESM Epilepsy-Specific Anti-
578 Seizure Medication

579   **TABLES**
580
581   Table 1. Sample Characteristics

Variable		Overall N = 916	Matched Levetiracetam Initiator N = 687	Other ESM Initiator N = 229	SMD
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

26

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
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