Antiseizure medications for post-stroke epilepsy: a real-world prospective cohort study

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**eTable 1**

**ASM regimens of each group**

| ASM                  | Older-generation ASM (prospective cohort) n=36 | Mixed generation ASM (prospective cohort) n=50 | Newer-generation ASM (prospective cohort) n=286 |
|----------------------|-----------------------------------------------|-----------------------------------------------|------------------------------------------------|
| CBZ                  | 23                                            | 17                                            | 250                                            |
| VPA                  | 7                                             | 1                                             | 13                                              |
| PHT                  | 2                                             | 1                                             | 2                                               |
| CBZ+VPA              | 1                                             | 1                                             | 5                                              |
| CBZ+PHT              | 1                                             | 1                                             | 1                                              |
| CBZ+CZP              | 1                                             | 1                                             | 1                                              |
| VPA+PB               | 1                                             | 1                                             | 1                                              |
| CBZ+LEV              |                                                |                                                |                                                |
| CBZ+LTG              |                                                |                                                |                                                |
| CBZ+ZNS              |                                                |                                                |                                                |
| CBZ+PER              |                                                |                                                |                                                |
| CBZ+PHT+GBP          |                                                |                                                |                                                |
| CBZ+PHT+LEV          |                                                |                                                |                                                |
| CBZ+LEV+TPM          |                                                |                                                |                                                |
| VPA+LEV              |                                                |                                                |                                                |
| VPA+ZNS              |                                                |                                                |                                                |
| VPA+LEV+LCM          |                                                |                                                |                                                |
| PHT+LEV              |                                                |                                                |                                                |
| PHT+LCM              |                                                |                                                |                                                |
| PHT+LEV+LCM          |                                                |                                                |                                                |
| CZP+LEV              |                                                |                                                |                                                |
| PB+LEV               |                                                |                                                |                                                |
| ZNP+LEV+CLB          |                                                |                                                |                                                |
| LEV                  | 230                                           |                                                |                                                |
| LCM                  | 13                                            |                                                |                                                |
| ZNS                  | 2                                             |                                                |                                                |
| LTG                  | 5                                             |                                                |                                                |
| GBP                  | 1                                             |                                                |                                                |
| LEV+LCM              | 2                                             |                                                |                                                |
| LEV+PER              | 3                                             |                                                |                                                |
| LEV+ZNS              | 3                                             |                                                |                                                |
Abbreviations: ASM, antiseizure medication; PER, perampanel; CBZ, carbamazepine; CZP, clonazepam; LEV, levetiracetam; LCM, lacosamide; LTG, lamotrigine; PB, phenobarbital; VPA, valproate; ZNS, zonisamide; CLB, clobazam; PHT, phenytoin; GBP, gabapentin; CZP, clonazepam; TPM, topiramate.

| Medication | Count |
|------------|-------|
| LEV+GBP    | 1     |
| LEV+TPM    | 1     |
| LTG+ZNS    | 1     |
| PER+ZNS    | 1     |

| Medication     | Count |
|----------------|-------|
| Older-generation ASM (retrospective cohort) n=69 | |
| CBZ            | 25    |
| VPA            | 21    |
| PHT            | 18    |
| VPA+PHT        | 3     |
| VPA+CBZ        | 1     |
| VPA+CZP        | 1     |
eTable 2
Mean daily dosage of ASM and proportion of adequate serum concentration of older-generation ASM at discharge*

| ASM        | Monotherapy ASM (mg/day) | Adequate serum ASM concentration (%) | Polytherapy ASM (mg/day) | Adequate serum ASM concentration (%) |
|------------|--------------------------|-------------------------------------|--------------------------|--------------------------------------|
|            |                          |                                     |                          |                                      |
| **Older-generation ASM** |                          |                                     |                          |                                      |
| CBZ (n=26) | 213.0 ±92.0              | 81.3%                               | 233.3 ±57.7              | 100%                                 |
| VPA (n=10) | 471.4 ±170.4             | 28.6%                               | 800.0 ±0                 | 100%                                 |
| PHT (n=3)  | 200.0 ±0                 | 0%                                  | 250.0 ±0                 | 100%                                 |
| PB (n=3)   | -                        | -                                   | 60.0 ±0                  | -                                    |
| CZP (n=1)  | -                        | -                                   | 0.5 ±0                   | -                                    |
| **Newer-generation ASM** |                          |                                     |                          |                                      |
| LEV (n=263)| 961.0 ±402.3             | -                                   | 1384.6 ±704.3            | -                                    |
| LCM (n=18) | 123.1 ±43.9              | -                                   | 160.0 ±54.8              | -                                    |
| ZNS (n=7)  | 200.0 ±0                 | -                                   | 260.0 ±89.4              | -                                    |
| LTG (n=6)  | 95.0 ±67.1               | -                                   | 150.0 ±0                 | -                                    |
| PER (n=4)  | -                        | -                                   | 4.0 ±1.6                 | -                                    |
| GBP (n=2)  | 800.0 ±0                 | -                                   | 300.0 ±0                 | -                                    |
| TPM (n=1)  | -                        | -                                   | 200.0±0                  | -                                    |

Data presented as mean ±standard deviation.

*Information of adequate serum concentration ASM of 10 cases in older-generation ASM could not be obtained.

Abbreviations: ASM, antiseizure medication; PER, perampanel; CBZ, carbamazepine; CZP, clonazepam; LEV, levetiracetam; LCM, lacosamide; LTG, lamotrigine; PB, phenobarbital; VPA, valproate; ZNS, zonisamide; PHT, phenytoin; GBP, gabapentin; CZP, clonazepam; TPM, topiramate.
## eTable 3

**Drug-related adverse effects causing dosage adjustment or discontinuation**

|                          | Older-generation ASM n=36 | Newer-generation ASM n=286 |
|--------------------------|---------------------------|----------------------------|
|                          | Dosage adjustment | Discontinuation | Dosage adjustment | Discontinuation |
| Skin eruptions           | 0                        | 1                        | 5                | 6              |
| Somnolence               | 1                        | 0                        | 0                | 0              |
| Dizziness                | 1                        | 0                        | 3                | 1              |
| Behavioral changes       | 1                        | 1                        | 0                | 3              |
| Abdominal symptoms       | 0                        | 0                        | 0                | 2              |
| Liver enzymes increase   | 0                        | 1                        | 0                | 1              |
| Others                   | 0                        | 1                        | 0                | 0              |
| total                    | 3 (8%)                   | 4 (11%)                  | 8 (2.8%)         | 13 (4.5%)      |

Abbreviations: ASM, antiseizure medication.
**eTable 4**  
**Patient characteristics of older-generation ASM (retrospective cohort)**

|                      | Older-generation ASM n=69 |
|----------------------|---------------------------|
| **Age, years, median (IQR)** | 72 (65-79) |
| **Female (%)**        | 20 (29)       |
| **Body weight, kg, median (IQR)** | 57 (50-65) |
| **Current alcohol consumption (%)** | 7 (10)       |
| **Family history of epilepsy (%)** | 1 (1)       |
| **Previous PSE (%)**  | 30 (43)       |
| **Previous ASM (%)**  | 23 (33)       |

**Comorbidities**

| Comorbidity          | Percentage |
|----------------------|------------|
| **Hypertension (%)** | 54 (78)    |
| **Dyslipidemia (%)** | 30 (43)    |
| **Diabetes (%)**     | 16 (23)    |
| **Chronic kidney diseases (%)** | 31 (45) |
| **Liver cirrhosis (%)** | 1 (1)     |
| **Atrial fibrillation (%)** | 26 (38) |
| **Dementia (%)**     | 25 (36)    |
| **Craniotomy (%)**   | 10 (14)    |

**Etiology of stroke subtype (%)**

| Subtype               | Percentage |
|-----------------------|------------|
| **Infarction (%)**    | 49 (71)    |
| **Cardiac embolism (%)** | 22 (32) |
| **Hemorrhage (%)**    | 22 (32)    |
| **TIA (%)**           | 1 (1)      |
| **SAH (%)**           | 3 (4)      |
| **Previous early seizure* (%)** | 2 (4) |

**Stroke lesion**

| Lobe                  | Percentage |
|-----------------------|------------|
| **Frontal lobe (%)**  | 13 (19)    |
| **Parietal lobe (%)** | 27 (39)    |
| **Temporal lobe (%)** | 25 (36)    |
| **Occipital lobe (%)**| 14 (20)    |
| **Cortical lesion (%)** | 51 (74) |

**Stroke size**

| Size      | Percentage |
|-----------|------------|
| <15 mm (%)| 16 (23)    |
| 15-30 mm (%)| 14 (20) |
| >30 mm (%)| 39 (57)    |

**Clinical course during hospitalization**
| Classification of seizures                                      |        |
|----------------------------------------------------------------|--------|
| Focal aware seizure (%)                                        | 6 (9)  |
| Focal impaired awareness seizure (%)                           | 21 (30)|
| Focal-to-bilateral tonic-clonic seizure (%)                     | 42 (61)|
| Others (%)                                                     | 0 (0)  |

| Detail of seizure                                              |        |
|----------------------------------------------------------------|--------|
| Focal or generalized motor seizure (%)                         | 49 (71)|
| Weakness (%)                                                   | 9 (13) |
| Aphasia (%)                                                    | 15 (22)|
| Amnesia (%)                                                    | 1 (1)  |

| EEG findings (n=62)                                            |        |
|----------------------------------------------------------------|--------|
| Focal slow wave (%)                                            | 36 (58)|
| Spike/sharp wave (%)                                           | 16 (26)|
| Rhythmic slow wave (%)                                         | 9 (15) |
| Periodic discharge (%)                                         | 4 (6)  |
| Hyperperfusion on SPECT (%) (n=48)                             | 33 (69)|
| Seizure-related hyperintensity on DWI (%) (n=64)               | 17 (27)|
| Hospitalization period, days, median (IQR)                    | 11 (8-16)|
| mRS at discharge, median (IQR)                                | 2 (1-4)|
| ASM combination therapy (%)                                    | 5 (7)  |

Abbreviations: ASM, antiseizure medication; IQR, interquartile range; PSE, post-stroke epilepsy; TIA, transient ischemic attack; SAH, subarachnoid hemorrhage; NIHSS, National Institutes of Health Stroke Scale; EEG, electroencephalogram; SPECT, single photon emission computed tomography; DWI, diffusion weighted image; mRS, modified Rankin Scale

Data are presented as median (interquartile range) or absolute (percentage) values.

*The history of early seizure was not available in 22 cases due to earlier admission in a different hospital.
eFigure 1
Kaplan-Meier curves of prospective newer-generation ASM (n=286) vs. prospective older-generation ASM (n=18) for seizure recurrence after eliminating subjects with inadequate or unknown serum concentration for older-generation ASM (n=18)

![Kaplan-Meier curve](image)

**Number at risk**

|               | Newer ASMs | Older ASMs |
|---------------|------------|------------|
| Days since discharge | 286 241 209 180 76 33 21 11 0 | 18 11 9 8 6 0 0 0 0 |

P<0.0001
eFigure2
Verification results of Kaplan-Meier curves for seizure recurrence, retention, and tolerability of ASM
(A-C) Kaplan-Meier curves of prospective newer-generation ASM (n=286) vs. retrospective older-generation ASM (n=69) for (A) time to seizure recurrence, (B) ASM discontinuation and dosage adjustment (retention), and (C) time to discontinuation of initial ASM regimen (tolerability).

(D-F) Kaplan-Meier curves of prospective newer-generation ASM (n=286) vs. prospective & retrospective older-generation ASM (n=105) for (D) time to seizure recurrence, (E) ASM discontinuation and dosage adjustment (retention), and (F) time to discontinuation of initial ASM regimen (tolerability).

Censored values are indicated by dots.
Mixed generation ASM group (n=50) was excluded in the analyses.