REVIEW OPEN ACCESS

Pathophysiology, Diagnosis, Prognosis, and Prevention of Poststroke Epilepsy

Clinical and Research Implications

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Abstract

Poststroke epilepsy (PSE) is associated with higher mortality and poor functional and cognitive outcomes in patients with stroke. With the remarkable development of acute stroke treatment, there is a growing number of survivors with PSE. Although approximately 10% of patients with stroke develop PSE, given the significant burden of stroke worldwide, PSE is a significant problem in stroke survivors. Therefore, the attention of health policymakers and significant funding are required to promote PSE prevention research. The current PSE definition includes unprovoked seizures occurring more than 7 days after stroke onset, given the high recurrence risks of seizures. However, the pathologic cascade of stroke is not uniform, indicating the need for a tissue-based approach rather than a time-based one to distinguish early seizures from late seizures. EEG is a commonly used tool in the diagnostic work-up of PSE. EEG findings during the acute phase of stroke can potentially stratify the risk of subsequent seizures and predict the development of poststroke epileptogenesis. Recent reports suggest that cortical superficial siderosis, which may be involved in epileptogenesis, is a promising marker for PSE. By incorporating such markers, future risk-scoring models could guide treatment strategies, particularly for the primary prophylaxis of PSE. To date, drugs that prevent poststroke epileptogenesis are lacking. The primary challenge involves the substantial cost burden due to the difficulty of reliably enrolling patients who develop PSE. There is, therefore, a critical need to determine reliable biomarkers for PSE. The goal is to be able to use them for trial enrichment and as a surrogate outcome measure for epileptogenesis. Moreover, seizure prophylaxis is essential to prevent functional and cognitive decline in stroke survivors. Further elucidation of factors that contribute to poststroke epileptogenesis is eagerly awaited. Meanwhile, the regimen of antiseizure medications should be based on individual cardiovascular risk, psychosomatic comorbidities, and concomitant medications. This review summarizes the current understanding of poststroke epileptogenesis, its risks, prognostic models, prophylaxis, and strategies for secondary prevention of seizures and suggests strategies to advance research on PSE.

Introduction

Cerebrovascular diseases account for approximately 50% of new-onset epilepsies in older adults (late-onset epilepsy).[1] Two to fourteen percent of survivors develop poststroke epilepsy (PSE) following ischemic stroke and 10%–20% following hemorrhagic stroke.[2] The onset latency of PSE is variable, although 40%–80% of cases with PSE emerge within the first year.[2] PSE is a critical determinant of stroke prognosis and is associated with a high risk of mortality, poor outcomes, and more extended hospital stay.[3] In addition, PSE, in conjunction with poststroke dementia, contributes to the complexity of stroke recovery, causing unplanned and costly

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Glossary

ASM = antiseizure medication; **BBB** = blood-brain barrier; **BEST** = Biomarkers, EndpointS, and other Tools; **CAA** = cerebral amyloid angiopathy; **CBZ** = carbamazepine; **CMB** = cerebral microbleed; **cSS** = cortical superficial siderosis; **HR** = hazard ratio; **ICH** = intracerebral hemorrhage; **IED** = interictal epileptiform discharge; **IL** = interleukin; **ILAE** = International League Against Epilepsy; **LEV** = levetiracetam; **LTG** = lamotrigine; **OR** = odds ratio; **PD** = periodic discharge; **POES** = postepilepsy stroke; **PROPOSE** = PROgnosis of POst Stroke Epilepsy; **PSE** = poststroke epilepsy; **RCT** = randomized controlled trial; **RDA** = rhythmic delta activity; **RR** = relative risk; **SAH** = subarachnoid hemorrhage; **TFNE** = transient focal neurologic episode.

hospital admissions, life-threatening emergencies, and social life restrictions.[3] Advances in acute stroke care are expected to increase the number of survivors in the European Union by 27% from 2017 to 2047.[4] We, therefore, need a collaborative effort toward drug discovery to prevent PSE. Early seizure, that is, a seizure within 7 days of stroke, is an independent predictor of PSE; however, additional variables, such as biological biomarkers and EEG, contribute to the increased risk of late seizures and can facilitate a better identification of patients with stroke who will eventually develop late seizures.[5] Animal studies suggested that poststroke inflammation, blood-brain barrier (BBB) disruption, and maladaptive plasticity lead to an epileptic focus. Currently, no antiepileptogenesis drugs that block these pathways are available.

Designing robust clinical trials to test potential antiepileptogenic agents has been challenging. The lack of data on human epileptogenesis-associated biological networks, the prohibitive costs, the logistic and ethical difficulties of testing hypotheses in multicentric international clinical trials, and the still limited experience with appropriate trial designs pose significant barriers to drug development mainly because a large patient population and a long follow-up period are needed.[6] Clinically, the presence or absence of seizures is a concern. The occurrence of seizures and the presence of epileptogenic factors do not necessarily align, and the likelihood of seizures can vary because of fluctuations in seizure thresholds. To date, EEG is considered the hallmark epilepsy biomarker; however, the presence of epileptiform discharges on EEG does not necessarily correlate with the manifestation of seizures.[7] When considering antiepileptogenesis, developing optimal biomarkers for epileptogenesis is crucial. Toward this goal, complying with the regulatory guidance for biomarker terminology and development, including Biomarkers, EndpointS, and other Tools (BEST) Resources from the US Food and Drug Administration-NIH Biomarker Working Group updated in 2021, is critical because it defines a response biomarker as one "that shows that a biological response has occurred in an individual exposed to a medical product or an environmental agent." A "response biomarker," which indicates early epileptogenic changes after stroke, can serve as a surrogate endpoint in antiepileptogenesis trials; if it is successfully validated and used early poststroke, it can shorten the duration required for patient follow-up. Per BEST, a prognostic biomarker is "used to identify the likelihood of a clinical event, disease recurrence or progression in patients with the disease or medical condition of interest." A "prognostic biomarker" can enrich antiepileptogenesis drug trials[8]; therefore, biomarker discovery and validation are critical to the design of clinical trials to test potential antiepileptogenic agents.[9]

This narrative review summarizes the current understanding of poststroke epileptogenesis, risks, prognostic models, primary and secondary prophylaxis, and proposes strategies to advance the research, particularly aimed at preventing PSE.

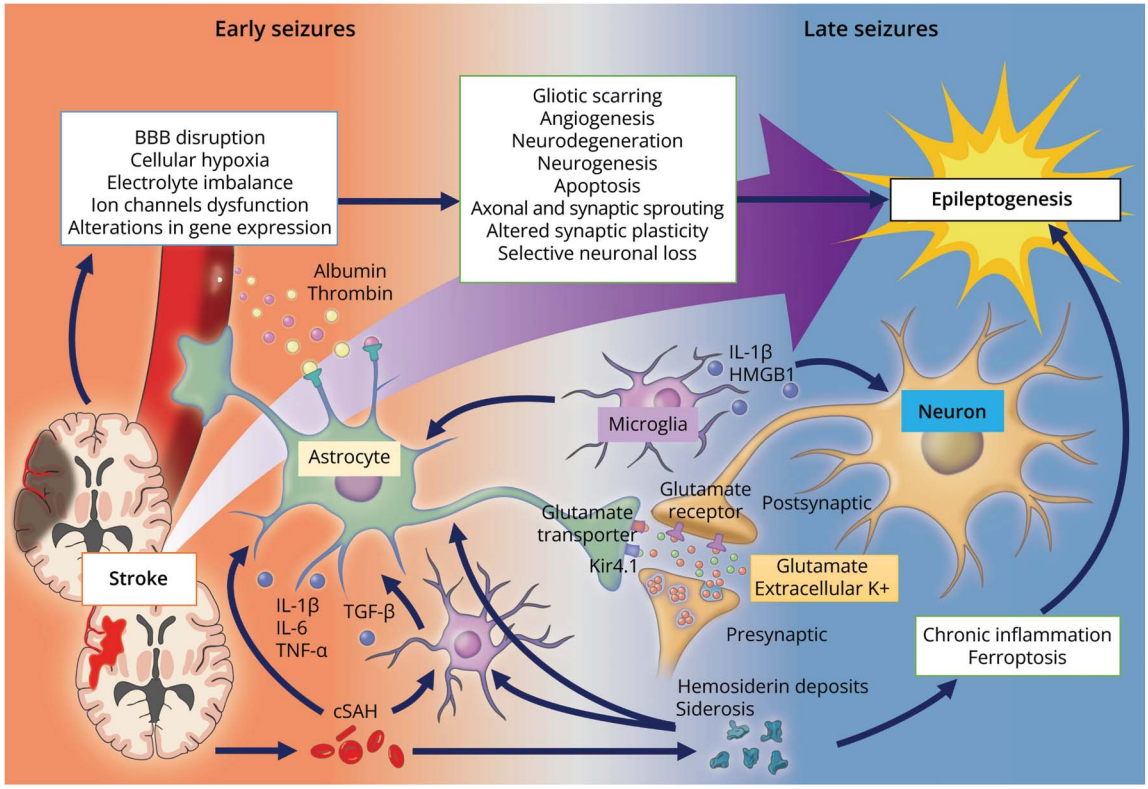
Pathophysiology

Distinguishing between early and late seizures should be based on pathophysiologic differences. Early seizures result from secondary tissue damage caused by stroke per se (Figure 1). No diagnostic tools are currently available to confidently determine whether epileptogenesis is ongoing and the time points at which the former mechanism ends, and the latter begins, as the exact biological mechanisms leading to late seizures remain elusive.[5] A tissue-based approach will prevent patient misclassification into early seizure and PSE, facilitate the selection of patients with PSE for primary prevention trials, and inform the precise time of the onset of epileptogenic pathology, which is critical because primary prevention requires administering an anti-epileptogenic agent before the onset of epileptogenesis.

For ischemic stroke, early seizures are associated with increased extracellular potassium and glutamate concentrations due to ischemic neuronal damage and, thus, increased neuronal excitation. By contrast, late seizures result from gliotic scarring within the cortex, neurovascular unit imbalance, and disruption of neuronal networks.[5] In animal studies, stroke-activated inflammatory cascades promote epileptogenesis. Activated astrocytes and microglial cells and the associated release of inflammatory cytokines (e.g., interleukin [IL]-1β and high mobility group protein B1) exacerbate BBB disruption, which in turn releases albumin and activates the transforming growth factor-β pathway, thereby initiating a vicious cycle.[5] These studies have only examined the early phase of stroke; hence, it remains unclear how this leads to the development of epileptogenesis.

Hemorrhagic stroke results in albumin leaking into the brain parenchyma, which induces epileptogenesis by the activation

Figure 1 Proposed Mechanisms of Acquisition of Epileptogenesis After Stroke



An illustration of epileptogenesis following stroke. Initially, stroke causes BBB disruption, cellular hypoxia, electrolyte imbalance, hemorrhagic transformation, and ion channel dysfunction, leading to early seizures. Subsequently, epileptogenesis can be acquired through secondary changes, such as gliotic scarring, angiogenesis, siderosis, and other pathologies. The time interval between early and late seizures is typically segregated at 7 days after stroke; however, the boundary between early and late seizures is not clearly defined but represents a continuous transition. Epileptogenesis is a complex process that involves multiple factors and mechanisms. BBB = blood-brain barrier; cSAH = convexity subarachnoid hemorrhage.

of the transforming growth factor-β receptor on astrocytes.[10] This process is mediated by a unique inflammatory pattern and the formation of excitatory synapses.[10] Pathogenic influence was also attributed to the extravasation of other blood born substances such as hemosiderin or iron. PSE is more common in hemorrhagic than ischemic strokes, suggesting the role of iron deposition in poststroke epileptogenesis. Iron is a trace element essential for mitochondrial function. Healthy adults store 4–5 g of iron, mainly in the erythrocytes and liver. Iron in the brain is tightly regulated to maintain cerebral homeostasis. Stroke disrupts this equilibrium and causes iron to accumulate in the brain parenchyma (e.g., intracerebral hemorrhage [ICH] or hemorrhagic transformation after ischemic stroke) or surface (e.g., subarachnoid hemorrhage [SAH]), which is highly cytotoxic. This newly discovered iron-dependent cell death, called ferroptosis, is attributed to lipid peroxidation caused by reactive oxygen species production. Iron overload is found in various neurologic diseases, including epilepsy. Persistent alterations in neuronal excitability may occur because of hemosiderin deposits, leading to post-ICH inflammation and gliosis.

Cortical superficial siderosis (cSS) is strongly associated with PSE.[11] Moreover, late seizures after ICH are associated with exclusively lobar cerebral microbleeds (CMBs) (hazard ratio [HR] 2.22; 95% CI 1.23–4.01) and APOEε4 genotype (HR 1.95; 95% CI 1.11–3.42), suggesting the coexistence of cerebral amyloid angiopathy (CAA) pathology in PSE.[12] A recent study reported that cSS is a predisposing factor for developing seizures in CAA.[13] cSS localized to the convexities of the cerebral hemispheres and supratentorial region may manifest as transient focal neurologic episodes (TFNEs; i.e., amyloid spells), which are mostly recurrent, stereotyped, and short-lasting (usually <30 minutes) and have various clinical features. TFNEs are found in 34% of patients of CAA with cSS and often occur repeatedly (53%), with 4% developing generalized seizures.[14] cSS can induce spontaneous seizures without other etiologies, suggesting that cSS is involved in poststroke epileptogenesis.

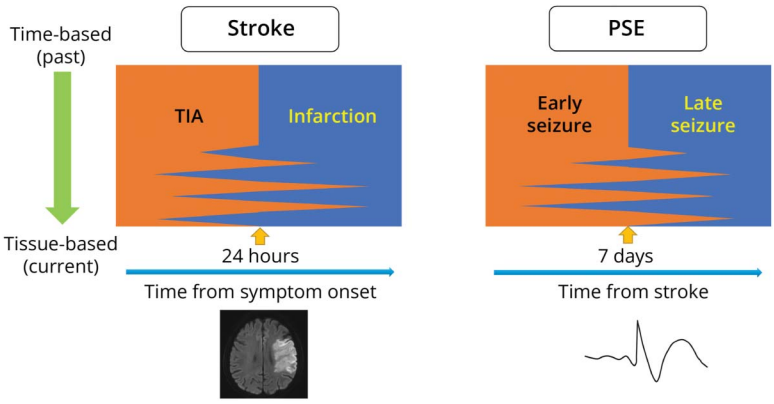
Diagnosis

The latest clinical definition of PSE by the International League Against Epilepsy (ILAE) considers unprovoked seizures occurring more than 7 days after stroke onset (late seizures) as PSE, due to their high risk of recurrent seizures.[5] However, since the pathologic cascade of stroke is not

uniform, it is possible for some cases to acquire epileptogenesis before the early seizure period (within 7 days of stroke onset). It has been shown that early seizures occurring 4–7 days after stroke were associated with a higher risk of developing PSE than those occurring within 3 days after stroke,[15] suggesting that the cutoff between early and late seizures is variable, and there may be patients with ongoing epileptogenic processes before the onset of early seizures (Figure 1). Hence, a tissue-based diagnostic approach to defining late seizures is warranted and will rely on discovering the hallmark biomarkers of poststroke epileptogenesis linked to late seizures (Figure 2). Similar to using a tissue-based diagnostic approach to define a transient ischemic attack (unlike the 24-hour cutoff for the symptom recovery),[16] a tissue-based diagnostic approach is currently desired to determine active epileptogenic processes and define PSE (instead of using the time cutoff to define late vs early seizures). Notably, there is currently limited evidence on how to apply the tissue-based approach to diagnosis, requiring further validation for optimal alignment with the ILAE definition.

There are various methods such as EEG, MRI, SPECT, magnetoencephalography, and biological biomarkers to assess epileptogenesis and diagnose PSE; however, EEG remains the most frequently used tool to examine PSE and plays pivotal roles in assessing the validity of epileptic seizures during interictal periods, estimating first seizure risk after stroke, evaluating further seizure recurrence risk, and predicting outcomes. Furthermore, the American Clinical Neurophysiology Society Standardized Critical Care EEG Terminology has proposed that specific interictal EEG findings indicate the presence of epileptic seizures.[17] For example, recent EEG studies have shown that interictal epileptiform discharges (IEDs), periodic discharges (PDs), and rhythmic delta activity (RDA) occurred in 29.8%, 19.2%, and 17.6% of patients admitted with PSE, respectively (eFigure 1).[18] Even before the development of PSE, a meta-analysis of 17 EEG studies reported ictal discharges in 8% (95% CI 4%–13%) and poststroke IEDs in 7% (95% CI 3%–12%).[19] The risk estimations of a first poststroke seizure by EEG have been reported as the 2HELPS2B score to guide short-term (7 days) primary prophylaxis in patients with spontaneous ICH.[20] This score includes the following variables: (1) 2H: frequency >2 Hz for any periodic or rhythmic pattern [1 point]; (2) E: sporadic epileptiform discharges [1 point]; (3) L: presence of lateralized PDs, lateralized RDA, or bilateral independent PDs [1 point]; (4) P: presence of "plus" features [superimposed, rhythmic, sharp, or fast activity] [1 point]; (5) S: prior seizure [1 point]; and (6) 2B: brief [ictal] rhythmic discharges [2 points]. To predict further seizures, a prospective study in acute stroke demonstrated that only IEDs and background activity asymmetry were significant predictors of subsequent late seizures, whereas PDs and RDA were not.[21] However, a study of PSE found PDs plus superimposed, admixed, or associated fast activity was significantly associated with functional decline at 6 months after discharge (crude odds ratio [OR] 3.20; 95% CI 1.03–9.96; eFigure 1).[22] Moreover, another study documented that status epilepticus meeting the criteria established by ILAE and Salzburg was associated with higher mortality and risk of PSE development in individuals with stroke and acute symptomatic seizures.[23] These findings suggest that the specific types of EEG findings reflect the presence of sustained neuronal excitation, indicative of epileptogenesis. Gamma frequencies and high-frequency oscillations are considered EEG markers of epileptogenicity and can potentially be detected on scalp EEGs. Owing to the pathophysiology of disrupted potassium channels in astrocytes and glutamate excitotoxicity in stroke,[5] wide-band EEG can record infraslow oscillations, including direct current shifts commonly reflecting elevated extracellular potassium. Continuous EEG monitoring (lasting ≥24 hours) was recommended especially in acute stroke patients with unexplained altered or fluctuating mental status or suspected seizure-like events in stroke unit due to the low IEDs detection rate with routine EEG (10–20 minutes).[24] In a study investigating detection of electrographic seizures with continuous EEG monitoring in critically ill patients including those with stroke,[25] the detection rates of electrographic

Figure 2 Early and Late Seizures: Shifting From a Time-Based to a Tissue-Based Approach



Although TIA was traditionally diagnosed based on the duration of symptoms (within 24 hours), current diagnostic criteria for TIA are tissue-based. Similarly, it is increasingly recognized that the distinction between early and late seizures should be tissue-based. Identifying epileptogenesis is crucial for selecting the most appropriate treatment strategy for PSE. PSE = poststroke epilepsy; TIA = transient ischemic attack.

seizures were 15% at the start of EEG, 56% within 1 hour, 77% within 1–6 hours, and reached 100% with continuous EEG over 168 hours. Thus, EEG findings can identify specific features for confirming epileptogenesis. However, focal irregular slow activity may not be the definitive clue in PSE because it could solely reflect stroke-induced tissue damage.

Risk Factors

Owing to the various etiologies and pathologies, the involvement of stroke-related risk factors is heterogenous (eTable 1); however, large stroke volume, cortical involvement, stroke severity, hemorrhagic stroke or hemorrhagic transformation, and early seizures are indisputable predictors of PSE.[5,24] Although early studies have attempted to distinguish early seizures from late seizures to investigate their risk factors, this approach may be challenging if using the time-based definitions.

Stroke treatments, including decompressive craniectomy, craniotomy, intravenous alteplase, or endovascular treatment, are also considered PSE risk factors. However, this finding was not replicated in the other studies, including large population-based stroke registries and well-designed multicenter studies, which reported no link between early seizures or PSE and reperfusion treatment, either intravenous thrombolysis alone or with mechanical thrombectomy.[26]

Differences in the severity or location of hemorrhagic transformation and patency of recanalized arteries may determine the occurrence of seizures following ischemic stroke. A meta-analysis of 51 studies demonstrated that regardless of whether patients with ischemic stroke undergo thrombolysis or thrombectomy, hemorrhagic transformation was significantly associated with early seizures (OR 2.58; 95% CI 1.63–4.10) and PSE (OR 2.23; 95% CI 1.11–4.49).[27] Recanalization therapy in patients with stroke may partially rescue dying neurons, leading to scattered surviving cortical "islands."[21] These islands may potentially affect epileptogenesis accompanied by hemorrhagic transformation.

Available data are contradictory and related to the significance of stroke location. In a large European multicenter study, acute symptomatic seizures following ischemic stroke were significantly associated with the posterior cerebral artery; however, no specific region was identified.[26] Small vessel disease-associated changes, including white matter lesions and lobar CMBs, are associated with PSE.[2,12] cSS strongly correlates with PSE, regardless of ischemic or hemorrhagic stroke,[11] and is characterized by hemosiderin deposition in the pial or subpial layers of the CNS. In SAH, cSS is associated with PSE regardless of aneurysm location, SAH severity, or stroke symptoms.[28] Moreover, a subarachnoid extension of ICH is significantly associated with early seizures, regardless of the hematoma location.[29] Such ICH extension can be accompanied by cSS. Structural MRI is therefore indispensable to evaluate hemosiderin deposits (cSS and CMB) using magnetic susceptibility-enhanced imaging, such as T2*-weighted imaging, and to predict PSE risks.

Omics approaches for biomarker discovery are promising. For example, using the omics approach to identify patients with greater genetic susceptibility or differentially expressed proteins linked to PSE can improve the selection of patients at risk of PSE. A systematic review found that 3 single-nucleotide variations, namely *TRMP6* rs2274924, *ALDH2* rs671, and *CD40* rs1883832, were significantly associated with an increased risk of PSE, whereas *AT1R* rs12721273 and rs55707609 were significantly associated with a reduced risk.[30] Stroke/TIA survivors with an elevated polygenic predisposition to epilepsy have a higher risk of developing PSE, suggesting a potential utility for polygenic risk scores.[30]

Blood biomarkers for determining the PSE risk have been reported but remain to be validated. In a comprehensive systematic review, 15 blood and 7 CSF biomarkers were significantly associated with post-brain injury epilepsy.[9] Enrichment analysis identified that the significant biomarkers (IL-6 and IL-1β) were predominantly associated with inflammation.[9] Although these analyses indicated the plausible role of inflammation in epileptogenesis, inflammation is likely not the only mechanism: methodological heterogeneity, bias, and insufficient validation of biomarkers were noted in the reported studies; therefore, more longitudinal studies are critically needed.[9]

Prognostic Models

PSE prediction models can enrich future antiepileptogenesis trials by determining high-risk patients. Previous studies have created separate scoring models for late seizure in ischemic and hemorrhagic strokes (Table 1). Some risk scores, such as the Post-Stroke Epilepsy Risk Score, integrate the risks for ischemic and hemorrhagic strokes.[31]

The PSEiCARe score consists of 7 items (prolonged hospital stay, seizure on stroke admission, elderly patients, intensive care unit stay, cognitive impairment, atrial fibrillation, and respiratory tract infection) and was proposed using big data from a medical insurance claims database in Taiwan.[32] This scoring system has been evaluated in the internal validation group and is unique because it includes dementia, atrial fibrillation, and pneumonia; however, it does not include imaging data regarding stroke.

According to a Swedish nationwide cohort study, hemorrhagic stroke was associated with approximately twice the cumulative PSE incidence compared with ischemic stroke (12.4% vs 6.4%) in >5 years.[33] Thus, creating separate models accounting for the pathophysiologic differences between ischemic and hemorrhagic strokes is desirable. For example,

1. The CAVE score (C: cortical hemorrhage; A: age <65 years; V: hematoma volume >10 mL; and E:

Table 1 Scoring Models for PSE

Type of stroke	Name	Year	Study design	Sample size	Validation	C-statistic	Rating scale items and respective scores (in brackets)
Ischemic and hemorrhagic stroke	PoSERS[a]	2010	Prospective	264	None	NA	1. Supratentorial lesions (2) 2. ICH (2), including cortical 3. Seizures occurring on or after day 15 poststroke (2) 4. Cerebral ischemia and persistent neurologic symptoms (1) 5. mRS ≥3 (1) due to sequelae from stroke 6. Seizures occurring within 14 d after stroke (1) 7. Cerebral ischemia in cortical or cortical-subcortical regions (1)
Ischemic stroke	PSEiCARe[a]	2018	Retrospective	125,757	None	0.76 (validation 0.79)	1. Prolonged hospital stay (>2 weeks) (1) 2. Seizure on admission (6) 3. Elderly patients (age ≥80 years) (1) 4. Intensive care unit stay on admission (3) 5. Cognitive impairment (dementia) (2) 6. Atrial fibrillation (2) 7. Respiratory tract infection (pneumonia) on admission (1)
	SeLECT	2018	Prospective	1,169	External validation	(validation 0.77)	1. Severity of stroke (NIHSS) 3 or less (0) 4–10 (1) 11 or more (2) 2. Large-artery atherosclerosis (1) 3. Early seizures (3) 4. Cortical involvement (2) 5. Territory of middle cerebral artery involvement (1)
	SeLECT-S	2022	Retrospective	1,070	Internal validation	0.84 (testing 0.83)	The SeLECT score + cortical superficial siderosis (6)
	SeLECT 2.0	2023	Retrospective	4,552	Internal validation	(validation 0.77)	Changing ES (3) to short ES (3) and acute symptomatic status epilepticus (7) in the SeLECT score
Hemorrhagic stroke	CAVE	2014	Retrospective	1,089	External validation	0.81 (validation 0.69)	1. Cortical hemorrhage (1) 2. Age <65 y (1) 3. Volume >10 mL (1) 4. Early seizures (1)
	CAVS	2020	Retrospective	2,507	Internal validation	(validation 0.76)	1. Cortical hemorrhage (1) 2. Age <65 y (1) 3. Volume >10 mL (1) 4. Surgical hematoma evacuation (1)
	LANE	2021	Retrospective	602	External validation	0.83 (validation 0.78)	1. Lobar hemorrhage (1) 2. Age <65 y (1) 3. NIHSS score ≥15 (2) 4. Early seizures (2)
	CAVE-S	2022	Retrospective	282	Internal validation	0.88 (testing 0.87)	The CAVE score + cortical superficial siderosis (1)

Abbreviations: ES = early seizure; ICH = intracerebral hemorrhage; mRS = modified Rankin scale; NA = not available; NIHSS = NIH Stroke Scale; PoSERS = Post-Stroke Epilepsy Risk Score; PSE = poststroke epilepsy.
For references related to each score model, refer to eAppendix 1.
[a] Late seizure is defined as ≥2 delayed seizures on or after 14 days poststroke (in PoSERS) and ≥2 delayed seizures on or after 7 days poststroke in PSEiCARe, and any seizures after hospital discharge (in CAVS). All the other scores defined an unprovoked seizure 7 days poststroke as a late seizure.

early seizures, 1 point each) helps predict epilepsy following a cerebral hemorrhage.[34] The incidence of epileptic seizures during 2.7 years (median) of follow-up was very high in patients with scores of 3 or 4 (34.8% and 46.2%, respectively).

2. The SeLECT score determines epilepsy risk for ischemic stroke (Se: severity 1 or 2 points; L: large-artery atherosclerosis 1 point; E: early seizure 3 points; C: cortical involvement 2 points; and T: territory of middle cerebral artery involvement 1 point).[35] The probability of delayed seizures within 5 years was 45%, 65%, and 83% for 7, 8, and 9 points, respectively, facilitating epilepsy risk stratification.

The SeLECT score has recently been updated (SeLECT 2.0), with current findings indicating that assessing through the

division of early seizures into short seizures and status epilepticus is more conducive to identify a high-risk PSE group.[23] Furthermore, based on the high contribution of cSS to PSE development, cSS was incorporated into the CAVE and SeLECT scores by adding 1 and 6 points, further improving PSE predictions (CAVE-S, SeLECT-S).[11] However, approximately half of the models have yet to be externally validated, and none of them exceed 90% accuracy. EEG findings have a diagnostic and prognostic value in patients with PSE, although those within 7 days of stroke onset are not considered independent risk factors for PSE.[26] Of note, there are still limited data on the diagnostic and therapeutic effect of these models, and we are not yet using them in treatment decisions. Further validation and examination of the clinical roles of these models are warranted.

Treatment

Primary Prophylaxis

Primary prophylaxis refers to preventing the occurrence of the first seizure after stroke. PSE impairs quality of life because it requires antiseizure medications (ASMs) with associated cognitive and other adverse effects, carries the risk of injury and sudden death from unexpected seizures, and imposes restrictions on work and daily life. In the American context, insurance premiums significantly increase if epilepsy is added to other cognitive and mobility issues after a stroke. It is uncertain whether seizures negatively affect neurorehabilitation, or whether ASMs, either prescribed prophylactically or therapeutically for early unprovoked seizures, result in worse rehabilitation outcomes, independently of the onset of epilepsy during treatment. The older-generation ASMs, including phenytoin and phenobarbital, could especially interfere with neural plasticity contributing to the recovery of behavioral and motor functions.[36] Thus, prevention of PSE is a critical issue for stroke survivors.

Antiepileptogenesis trials are challenging, and evidence from randomized controlled trials (RCTs) for the effectiveness of primary prophylaxis with ASMs is insufficient. The European Stroke Organization guidelines suggest against the general primary ASM prophylaxis administration owing to sparse reliable evidence.[37] Four completed antiepileptogenesis trials meet the current standards of an RCT design.

1. In a randomized double-blind study comparing 1-month valproic acid treatment and placebo each administered 2 hours after stroke onset for primary seizure prevention, including 72 adults with intracerebral hemorrhage, the risk of poststroke seizures up to 1 year (relative risk [RR] 0.88; 95% CI 0.35–2.16) or death (RR 1.20; 95% CI 0.40–3.58) did not differ.[38]
2. In a randomized double-blind study comparing a 3-day diazepam treatment with a placebo for primary seizure prevention up to 3 months after stroke in 784 adults with acute stroke, there was no evidence of a difference in the risk of poststroke seizures for all stroke groups and subgroups of hemorrhagic or ischemic stroke (RR for all stroke, 0.47; 95% CI 0.18–1.22).[39] In a subgroup analysis of anterior circulation cortical infarcts, primary prophylaxis with diazepam was associated with a reduced risk of poststroke seizures (RR 0.21; 95% CI 0.05–0.95). Mortality risks did not differ between the diazepam and placebo groups at the 2-week (RR 0.84; 95% CI 0.56–0.26) and 3-month (RR 0.95; 95% CI 0.72–1.26) follow-ups.[40]
3. In a multicenter, randomized, placebo-controlled, double-blind study of Early Treatment with Levetiracetam After Stroke for the prevention of late seizures, only 16 patients (levetiracetam [LEV], n = 9; placebo, n = 7) were included, and only 1 patient (placebo group) developed PSE.[41] Recognizing and assessing the occurrence of epileptic seizures was difficult because benzodiazepines and ASMs were prescribed mainly by other treating physicians, and adverse effects might have been related to the stroke or comedication initiated before or at the onset of stroke rather than the study medication. A prophylactic study assessing the antiepileptogenic efficacy of a short ASM treatment period may not be feasible owing to the challenge in recruiting a sufficient number of participants or determining PSE seizure episodes.
4. Most recently, a randomized, double-blind, placebo-controlled, phase 3 trial (PEACH) showed significant LEV effects in preventing electrographic seizures in acute phase (≤72 hours) of ICH but did not prevent clinical seizure manifestations, reflecting the formation of epileptogenesis.[42]

No reliable biomarkers of epileptogenic changes aiding in selecting patients with a high risk of PSE currently exist; however, risk scores, such as the CAVE and SeLECT scores, would help in patient stratification for such trials.[37] Determining trial enrichment strategies is critical to ensure that patients with a greater likelihood of developing PSE are enrolled. A small proportion of patients with stroke develop PSE after a long latent period; thus, an antiepileptogenesis trial requiring extended follow-up would be expensive since the antiepileptogenic effects of any compound can only be assessed following treatment cessation.

Considering the complexity of an antiepileptogenic study, repurposing an existing compound in clinical use for treating epilepsy or any other condition seems to be the only realistic option.[39] A recent meta-analysis of 6 studies investigating the effects of statin use to prevent the development of PSE suggests that statin use lowers the risk of PSE (OR 0.60; 95% CI 0.42–0.84) and early seizures (OR 0.36; 95% CI 0.42–0.84) remarkably.[43] Double-dose statin (40 mg atorvastatin or 20 mg rosuvastatin per day) lowered the frequency of

developing PSE more than the standard dose did.[44] Possible mechanisms for the prophylactic effect of statins include anti-inflammatory effects on the vascular endothelium, free radical generation inhibition, GABAergic activity activation, and cellular membrane stabilization. However, the effect of statin remains to be confirmed in RCTs with a high level of evidence. Moreover, if patients with stroke with a 50% or greater risk of developing late seizure are identified using the CAVE or SeLECT score, administering ASMs as primary prophylaxis may be feasible, although this remains to be confirmed in clinical trials.

Strategies for Secondary Prophylaxis

Secondary prophylaxis aims to prevent further seizures following the first seizure in stroke survivors. After the acquisition of epileptogenesis, the use of ASMs for secondary prophylaxis in PSE is generally recommended to alleviate the high seizure recurrence rate in PSE.[37] However, evidence specifying the most appropriate ASMs is very limited because few high-quality RCTs exist.[40] A nationwide cohort study in Sweden showed that lamotrigine (LTG) and LEV had higher retention rates than did carbamazepine (CBZ) in PSE.[45]

The PROgnosis of POst Stroke Epilepsy (PROPOSE) study, a prospective multicenter observational cohort study, suggested that newer-generation ASMs could be more effective, compared with older-generation ASMs, for treating PSE in ASM retention and seizure recurrence prevention.[46] The HR for newer-generation ASMs was 0.47 (95% CI 0.29–0.81) compared with that of older-generation ASMs, although previous meta-analyses of 5 studies (1,425 participants) found no significant superiority of newer-generation over older-generation ASMs in seizure control in older adults with new-onset epilepsy.[47] In the PROPOSE study, ASMs were prescribed at the physicians' discretion, which could explain the underdosing of older-generation ASMs to avoid serious adverse effects owing to their narrower safety range.[46] However, many other factors may have influenced the conflicting results between studies, including more frequent drug-drug interactions with older-generation ASMs than with newer-generation ASMs, and ethnic differences in the effectiveness, pharmacokinetics, and adherence between older-generation and newer-generation ASMs.

The few drug-drug interactions of newer-generation ASMs than older-generation ASMs are relevant for PSE owing to the many comorbidities in older age, such as hypertension, diabetes mellitus, dyslipidemia, and cardiac and renal diseases, mandating multiple drug treatments in this population. The effect of older-generation ASMs on anticoagulants prescribed for the prophylaxis of cardioembolism could be life-threatening in patients with atrial fibrillation. The concept of postepilepsy stroke (POES) was proposed,[48] which could be partially attributable to older-generation ASMs (Table 2). In a study comparing cases of seizures occurring in individuals

Table 2 Potential Factors of Older-Generation ASMs for POES

Older-generation ASMs	Mechanisms	Potential influences	Effect on POES	Monitoring
CBZ **PHT** **PB**	CYP450 induction (direct effects)	HMG-CoA reductase ↑ Reduction in cholesterol transformation in bile acids	Total cholesterol, triglycerides, and LDL↑	Blood tests
		Vitamin B6↓	Homocysteine ↑	Blood tests
	CYP450 induction (indirect effects: a decrease of concentration of a drug metabolized by CYP450)	Statins↓	Total cholesterol, triglycerides, and LDL↑	Blood tests
		Antithrombotic drugs ↓ (Warfarin, DOACs: rivaroxaban, dabigatran, and apixaban)	Anticoagulant effect ↓	Blood tests
		Antihypertensive drugs ↓	Blood pressure ↑	Blood pressure monitoring
	Sodium channel block	Sinus bradycardia Sinus pauses AV block	Risks of cardiac embolism ↑	ECG
	Unknown	Unknown	Lp(a) ↑ Carotid intima-media thickness ↑	Blood tests Carotid echo
CBZ	Unknown	ADH↑	Blood pressure ↑ Congestive heart failure	Blood pressure monitoring Cardiac echo
PHT	Insulin secretion↓	Blood sugar ↑	HbA1c ↑	Blood tests
VPA	Insulin secretion↑	Weight gain (up to 70%)	Metabolic syndrome	Blood tests Body weight measurement

Abbreviations: ADH = antidiuretic hormone; ASM = antiseizure medication; AV = atrioventricular; CBZ = carbamazepine; CYP = cytochrome P450; DOAC = direct oral anticoagulant; HbA1c = hemoglobin A1c; HMG-CoA = 3-hydroxy-3-methylglutaryl coenzyme A; LDL = low-density lipoprotein; LP(a) = lipoprotein a; PHT = phenytoin; POES = postepilepsy stroke; VPA = valproic acid.

aged 60 years and older with age-matched controls from the UK General Practice Research Database, the RR of stroke was 2.89 (95% CI 2.45–3.41).[49] Another case-control study also reported that adult patients with epilepsy had a 60% higher risk of stroke compared with controls.[50] In general, ASMs that induce cytochrome P450 activity can affect common medications for stroke and directly influence lipid metabolism. Individuals administered enzyme-inducing ASMs such as CBZ or phenytoin had significantly increased levels of serum total cholesterol and low-density lipoprotein cholesterol compared with those not taking ASMs.[51] These ASMs may induce dyslipidemia, increasing the risk of stroke recurrence in patients with PSE, although it may not necessarily promptly aggravate the clinical course of vascular impairment and disease. Considering LEV, the European Heart Rhythm Association has noted effects on direct oral anticoagulants owing to potential P-glycoprotein–mediated drug-drug interaction; however, this is only based on results from animal models. However, sodium-channel blocker ASMs might affect cardiac conduction and should be monitored using ECG. Therefore, POES is essential for physicians to treat patients with PSE comprehensively.

Circulatory system disorders are the leading cause of death in patients with PSE. A large cohort study on ASM monotherapy treatment for PSE in Sweden (n = 2,577) reported a lower risk of cardiovascular death with LTG (HR 0.76, 95% CI 0.61–0.95) and LEV (HR 0.77, 95% CI 0.60–0.99) than with CBZ.[52] Drug-drug interactions may have contributed to this, although the direct causal relationship between PSE and deaths often remains unknown. Numerous studies have indicated that in clinical practice, a significant number of patients with PSE are not seizure-free and the treatment patterns are suboptimal, with a modest number of patients still receiving enzyme inducers. However, another study reported that individuals with high vascular risk factors were more likely to develop epilepsy,[53] although the causality is not definitive. Future studies must clarify the drug-drug interactions and long-term biological effects of ASMs that potentially underlie POES, especially for newer-generation ASMs owing to the relatively less experience in clinical use compared with older-generation ones.

Significance of Seizure Control for Prognosis

A nationwide cohort study in Sweden revealed that PSE had a significantly increased risk of all-cause mortality (HR 1.68; 95% CI 1.25–1.53),[33] which remained elevated after adjusting for various factors, such as age, comorbidities, and stroke severity. A cohort study in Taiwan reported a mortality rate of approximately twice as high for patients with PSE as that for patients with stroke without epilepsy and more than 4 times higher than that for the healthy population.[54] PSE was an independent predictor of mortality among patients with ICH in a population-based cohort study with a median follow-up of 8.8 years in Finland (HR 1.41; 95% CI 1.06–1.87).[55]

In general, PSE is often considered to exhibit favorable responsiveness to ASMs compared with other forms of focal

Table 3 Recommendations for Future Clinical Research

Diagnosis and prognostic models	Biomarker discovery	Identify and validate epileptogenesis biomarkers per the US FDA Context of Use requirements
	High-quality data collection	Define common data elements specific to the PSE research and collect them comprehensively and accurately
	Algorithm development	Develop advanced algorithms to recruit PSE research participants
	Generalization	Collaborate globally on multicentric studies
	Clinical validation and collaboration	Collaborate on multicentric studies
Prophylaxis	Accurate screening strategies	Develop and use optimal patient screening tools for PSE research
	Stratification of risks of PSE	Classify the risks of PSE before conducting research
	Optimal treatment timing	Investigate the optimal timing for initiating primary prophylaxis
	Cost-effectiveness analysis	Determine the economic effect of primary prophylaxis
	Generalization	Collaborate globally on multicentric studies
	Clinical validation and collaboration	Collaborate on multicentric studies
Seizure management	Long-term treatment effects	Investigate the long-term effect of ASMs on POES
	Personalized treatment	Develop individualized treatment plans
	Economic evaluation	Conduct cost-effectiveness and cost-benefit analyses
	Generalization	Collaborate globally on multicentric studies
	Clinical validation and collaboration	Collaborate on multicentric studies

Abbreviations: ASM = antiseizure medication; FDA = Food and Drug Administration; POES = postepilepsy stroke; PSE = poststroke epilepsy.

epilepsies; however, achieving a completely seizure-free state is not always attainable (>30% experience a seizure recurrence).[56] Considering seizure recurrence in PSE, functional disability, assessed with the modified Rankin scale, was more likely to worsen with seizure recurrence (adjusted OR 3.26; $p = 0.01$).[57] Furthermore, frequent seizures were associated with worse functional decline ($p = 0.006$ for trend).[57]

The onset of seizures in young stroke survivors increases the risk of progression to dementia.[58] A comprehensive meta-analysis of 37,420 patients with poststroke seizures and 1,840,906 patients without poststroke seizures (N = 72 journal articles) found that patients with poststroke seizures are at significantly high dementia risk (OR 3.1; 95% CI 1.3–7.7) and odds for mortality (OR 2.1; 95% CI 1.8–2.5) and poor outcomes (OR 2.4; 95% CI 1.9–3.1).[3] Although the exact mechanism is unknown, repetitive clinical seizures may cause permanent damage to the brain, or using ASMs may impair cognitive function. Furthermore, cognition can also be affected by multiple factors such as the stroke lesion itself, adverse effects of ASMs, drug interactions, social restrictions that affect mood, and changes in environmental factors owing to seizures. In the Atherosclerosis Risk in Communities study, which investigated risk factors for late-onset epilepsy in midlife among over 10,000 individuals, the most impactful risk factors were stroke (HR 3.47; 95% CI 2.85–4.23) and dementia (HR 2.68; 95% CI 2.19–3.28).[59] Stroke, dementia, and epilepsy are closely related influencing, intermingling, and forming a vicious cycle.

PSE is a critical stroke prognosis determinant, and its prevention should be a high priority. Most previous studies on stroke prognosis have not considered seizures and seizure outcomes, and despite the need for comprehensive care poststroke, physicians typically prioritize efforts to prevent stroke recurrence. The prognostic importance of seizure prevention should be further recognized in stroke survivors.

Prospects for Future Research

Stroke, dementia, and epilepsy form a disease triangle among older individuals in this rapidly aging society. Since no cure for PSE is available, the best strategy is to prevent stroke occurrence and recurrence in stroke survivors. However, emerging lines of evidence strongly emphasize the prognostic importance of seizure prevention in stroke survivors. Moreover, many questions remain to be addressed in the field of PSE, including methods for identifying the acquisition of epileptogenesis after stroke, feasible prophylactics in high-risk groups, and the best ASM regimen for secondary prophylaxis. Since conducting large-scale studies of PSE is challenging, multicenter and international collaboration studies are needed (Table 3).

Therefore, the International Post Stroke Epilepsy Research Consortium[60] was convened with the following goals: promote collaboration between scientists active in stroke and epilepsy research, build and disseminate evidence needed to optimize care for patients with PSE, promote collaborative efforts to validate preclinical models, support clinical trials that test neurotherapeutics to prevent and manage PSE, and build a platform to anchor multicenter studies for PSE research. Further efforts toward developing preventive measures for epilepsy in stroke survivors are urgently warranted. Policymakers, including stroke and epilepsy organizations, should join forces with PSE researchers and patient organizations to promote PSE prevention research regionally and globally.

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Appendix *(continued)*

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