

Vascular Epilepsy

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ARTICLE INFO

Received Date: May 28, 2021

Accepted Date: October 01, 2021

Published Date: October 04, 2021

KEYWORDS

Seizure
Epilepsy
Vascular
EEG
MRI

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Citation for this article: Oumerzouk J, Louhab N, Chraa M and Kissani N. Vascular Epilepsy. Neurological Disorders & Epilepsy Journal. 2021; 4(2):143.

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ABSTRACT

Seizures can be a presenting feature of acute stroke. They may complicate its early clinical course or be a late complication or sequela. The incidence of combined “early” and “late” seizures after stroke has been reported to be approximately 10% and the prevalence is between 2-4%. Mechanisms leading to poststroke seizures and chronic epilepsy in both ischemic and hemorrhagic strokes are diverse. Focal slowing or diffuse slowing activities, as well as rhythmic slow waves are associated with a low risk of early onset seizures whereas focal spikes, sharp waves, periodic lateralized, or periodic bilateral discharges are associated with a higher risk.

There are no randomized controlled trials performed in stroke patients evaluating management strategies for poststroke seizures and epilepsy. Treatment options should be extrapolated from those of epilepsy in general, taking into consideration hepatic and renal function, tolerability, costs, interactions between Antiepileptic Drugs (AED), interactions with antithrombotic medication and other treatments. However, randomized controlled trials of AED prophylaxis for acute and late onset seizures are essential to improve the evidence level of current guidelines and recommendations for the management of post-stroke seizures

INTRODUCTION

-Seizures can be a presenting feature of acute stroke. They may complicate its early clinical course or be a late complication or sequela. Stroke and other vascular lesions of the brain, including subcortical vascular encephalopathy, are the main cause of epilepsy in old age [1-3]. We define poststroke seizure as “single or multiple convulsive episode/s (fit/s) after stroke and thought to be related to reversible or irreversible cerebral damage due to stroke regardless of time of onset following the stroke” and Post-Stroke Epilepsy (PSE) as “recurrent seizures following stroke with confirmed diagnosis of epilepsy” [1,2].

INCIDENCE AND PREVALENCE OF POST STROKE SEIZURES

The Frequency of Seizures and Epilepsy in Stroke

Poststroke seizures and Poststroke epilepsy constitute important complications in patients surviving a stroke, and stroke has been long recognized to be a common cause of epileptic seizures. Indeed, stroke represents the most common cause of new-onset seizures and epilepsy in adults aged ≥ 60 years accounting for 25-50% of new onset symptomatic epilepsy. Early onset seizures occur within 7 days of stroke, whereas late onset seizures occur after 7 days of stroke onset. The incidence of

combined “early” and “late” seizures after stroke has been reported to be approximately 10% and the prevalence is around 2-4%. The 5-year risk of Poststroke seizures ranges from 7% to 11%.

In addition, stroke is one of the most frequent etiologies of Status Epilepticus (SE), although this condition occurs in only 1.5% of strokes [1-3].

The Relationship between Early and Late Seizures

-The occurrence of early seizures increases the risk of subsequent epilepsy, but epilepsy develops in a minority of cases only (about one third). In addition, if a late seizure occurs, the risk of subsequent epilepsy is much higher [1,4,5].

CLASSIFICATION [2,3,5]

Table 1: Classification of vascular seizures and epilepsy [1-4].

| Type of seizure | Clinical characteristics |
|--|--|
| Acute seizure | <ul style="list-style-type: none"> -Epileptic seizure occurring within the first 24 h after onset of stroke; 40% of the seizures after ischemic stroke and 57% of the seizures after hemorrhagic stroke, occurred within 24 hours of onset. -Other causes and precipitants of seizures, either in the brain or systemically (e.g. hypoglycemia, hypoxia, hypocalcaemia, meningitis and the proconvulsant effect of treatments) should be excluded. -Patients with a first acute provoked post-stroke seizure have a risk of a subsequent recurrent seizure over the following 10 years of around 30%, whereas patients with a first unprovoked seizure have a risk of 70%. -They can be either partial or generalized. Partial seizures are more frequent, and are usually motor seizures, sometimes with secondary generalization |
| Early poststroke seizure | <ul style="list-style-type: none"> -One or more seizures within 1 week or 2 weeks (1-15 days) after the stroke and most are single seizures. -Approximately a third of poststroke seizures occur in the early phase -Occurred in 4.8% of ischemic stroke patients and in 7.9% of hemorrhagic stroke patients - Usually present with a focal onset, arising from areas in close proximity to the area of infarcted tissue -After the first early post-stroke seizure, the risk of recurrence is estimated to be 10–20% |
| Late poststroke seizure | <ul style="list-style-type: none"> -One unprovoked epileptic seizure at least 2 weeks after the stroke and have a peak within 6 to 12 months after the stroke and have a higher recurrence rate of up to 90% in both ischemic and hemorrhagic stroke. -Occurred in 3.8% of ischemic and 2.6% of hemorrhagic stroke patients. -Are often generalized tonic-clinic seizures. -Late seizures may be associated with a higher likelihood of epilepsy |
| Poststroke epilepsy/recurrent seizures | <ul style="list-style-type: none"> -Occurred in 2.5% of the patients. - Initially defined as two or more unprovoked epileptic seizures occurring at least 2 weeks after the stroke (ILAE). Actually, according to the latest revised classification of the International League Against Epilepsy (ILAE), a late-onset seizure in the context of stroke defines vascular epilepsy, making it no longer necessary to wait for a second seizure. Thus, it is no longer necessary to wait for seizure relapse before starting antiepileptic drug treatment. |
| Status Epilepticus | <ul style="list-style-type: none"> - Occurs in only 0.14–1.1% of strokes -May the first epileptic symptom of stroke in 0.12% of cases or it can follow one or more single seizures -Stroke is the most common aetiology for status epilepticus in the elderly (22% of new-onset status epilepticus are related to stroke) and occurs more often among patients with disabling strokes: the type of stroke, topographic findings, size of the lesion, or Electroencephalographic (EEG) pattern do not predict the progression to status epilepticus -Early-onset status is more often nonconvulsive than convulsive. |

Pathogenesis

Conventionally, epilepsy is regarded as arising from cortical regions. However, subcortical changes as seen in cerebrovascular small vessel disease, may contribute to epileptogenesis. Mechanisms leading to poststroke seizures and chronic epilepsy, in both ischemic and hemorrhagic strokes, are diverse:

- The mechanism of early seizures associated with stroke include the changes in the penumbra zone, brain edema,

the effects of ischemia (global hypoperfusion can also cause seizure activity, particularly in sensitive areas such as the hippocampus, a well known epileptogenic area), metabolic changes (breakdown of membrane phospholipids, and release of free fatty acids), alterations in neurotransmission (ischemia released excitatory amino acids, mainly glutamate, producing a cascade of toxic events; down-regulation in the efficacy of GABAergic intracortical inhibition with subsequent NMDA-receptor-mediated excitation), and finally, the alterations in

intracellular ions (reduction of the blood flow leads to subsequent cytotoxic effects with an accumulation of intracellular calcium and sodium, resulting in depolarization of the cellular membrane and lowering of seizure threshold) [1,3,5,6].

- The mechanisms of late-onset seizures and poststroke epilepsy are associated with later changes in the structure and function of cerebral tissue, the formation of abnormal scar with reorganization of axonal connections, loss of GABA-mediated inhibitory pathways and changes in the properties or composition of the glutamate receptor subunits. The presence of hemosiderin and iron in cortical neurons (iron inhibits glutamate reuptake into astrocytes), free radical formation and membrane peroxidation, selective neuronal cell death and apoptosis, changes in membrane properties, mitochondrial changes, receptor changes (e.g. loss of GABAergic receptors), deafferentation, and collateral sprouting (both at the site of ischemia as well as in remote areas) [3,4,7].

RISK FACTORS OF POST-STROKE-SEIZURES AND EPILEPSY [1,2,4,6,7]

Etiologies of Vascular Seizures and Epilepsy

Subarachnoid hemorrhage (SAH): Patients with SAH or those with cerebral venous thrombosis, have a higher rate of seizures than ischemic stroke patients [3,5]. Early seizures after admission to hospital complicate the clinical course of 4–10% of patients admitted for SAH. Hemiparesis, cerebral infarct, the clinical and imaging severity of the bleeding, intraparenchymal hematoma and an aneurysm as the cause of bleeding predict the likelihood of post-stroke seizures. Their occurrence is thought to be related to the amount of blood in the basal cisterns, which are in direct contact with the frontal and temporal lobes [1,4,8].

Table 2: Risk Factors of poststroke seizures and epilepsy [1-4].

| Risk factors patient related (demographic variables, vascular risk factors) | Risk factors stroke related, both clinical (symptoms/signs, severity and dependency) and radiological (stroke type, location and size) | Risk factors related to comorbid conditions | Risk factors related to seizures |
|--|---|--|--|
| -Demographic variables: younger patients, men -Risk factors for vascular disease: hypertension, smoking, diabetes, raised serum total cholesterol, heavy alcohol abuse and lack of exercise. -All these factors, have been associated with the development of seizures or epilepsy, even in the absence of overt stroke. | <p>- Clinic:</p> <ul style="list-style-type: none"> *Loss of consciousness, confusional syndrome and persistent paresis *Severe and disabling strokes (NIHSS score >4 at the stroke presentation) independently of the size of the ischaemic lesion on CT scanning, perhaps because the ischaemic penumbra, not visualized on CT, is epileptogenic. *Neurological and medical complications *Stroke recurrence * The severity of persistent disability after the stroke *Seizures were more often associated with cardioembolic than with large-vessel atheroma or small-vessel disease. <p>-Imaging:</p> <ul style="list-style-type: none"> *Lobar haemorrhage, haematoma size, hemorrhagic transformation of ischaemic lesions, total anterior circulation infarcts, infarcts larger than one-half of the hemisphere, large infarcts, infarcts involving more than one lobe, and multifocal infarcts. *Cortical involvement, especially if the infarct has an anterior hemispheric location; 'watershed' topography; irregular borders and areas of incomplete destruction. *Large combined cortical and subcortical infarct, hippocampus involvement * involvement of the middle cerebral artery (MCA) territory, involvement of the parieto-temporal cortex, supramarginal gyrus, and superior temporal gyrus <p>NB: Lacunar, subcortical, and posterior circulation infarcts are infrequently associated with the development of epilepsy</p> | <ul style="list-style-type: none"> -Myocardial infarction, peripheral vascular disease, large-artery atherosclerosis, cerebrovascular disease and left ventricular hypertrophy -APOE e4 allele, dementia -Global and regional brain atrophy | <ul style="list-style-type: none"> - Clinic: Early seizure (≤ 7 days) -EEG: Focal spikes, sharp waves, diffuse slowing, periodic lateralized, or periodic bilateral discharges, FIRDAs |

PLEDs = periodic lateralized epileptiform discharges

FIRDAs = Frontal intermittent rhythmic delta activities

Intracerebral hemorrhage (ICH): ICH is associated with the highest incidence of post-stroke seizures (10.6%-15.4% of them develop the condition). Factors which are predictive of early and/or late-onset seizures include younger age, the severity of neurological deficits, lobar (cortical) hemorrhage, hemorrhage location within the cerebrum, greater volume of hematoma, Subarachnoid Hemorrhage (SAH), subdural hematomas and surgical hematoma evacuation (an open surgery can be expected to add neuronal injury to an already damaged area, increasing the risk of seizure). These criteria call for prophylactic Antiepileptic Drugs (AEDs) [1,2,5,7].

The epileptogenesis process in early seizures is explained by a space-occupying lesion with a resulting mass effect, focal ischemia and direct cellular dysfunction from blood products, while in late seizures, it is caused by gliotic scarring, hemosiderin deposition, neuronal reorganization, and neurodegeneration, with the hemorrhage no longer present. In ICH, there is no evidence that either the amount of blood present in the brain parenchyma, or the amount of blood in the cisternal and ventricular spaces seems to influence the occurrence of seizures [3,4,5].

Cerebral arteriovenous malformations (AVMs): Epilepsy is the second most frequent presentation for all AVM patients, but its importance is often overlooked in favour of intracranial hemorrhage, which is the most frequent and feared component of an AVM's natural history. Various patient and nidus characteristics are linked to AVM-associated epilepsy, including male gender, younger age, larger unruptured AVM size, cortically based frontal or temporal nidus location, superficial AVM topography, AVM location at an arterial border zone, absence of intranidal aneurysms, presence of a venous varix, nidus supply by the middle cerebral artery, or the external carotid artery, or a cortical irrigating artery, as well as cortical, temporal superficial, or parietal superficial nidus locations. Patients harboring such nidi likely warrant more rigorous neurological monitoring for signs of epilepsy [1,4,5].

AVM intervention (surgery, radiosurgery, and embolization) appears to afford favorable seizure outcomes in the majority of patients with AVM-associated epilepsy. Although in some studies, seizure remission appears to correlate with complete nidus obliteration [2,3].

Cerebral vein and dural sinus thrombosis: -Seizures are a frequent inaugural manifestation of cerebral vein and dural sinus thrombosis (10–61%). Seizures can be focal, generalized or both. Some patients experience late-onset and, less often, recurrent seizures after the acute phase. In some reports, remote seizures occurred only in patients with early seizures associated with hemorrhages diagnosed by CT/MRI on admission [1,11].

Ischaemic strokes: 6.5% to 8.5% of ischemic strokes develop post-stroke seizures.

Stroke in young adults: Lupus, other vasculitides, and the use of recreational drugs can cause both strokes and seizures [2,8,10].

Cerebral amyloid angiopathy: It remains unclear whether seizures reflect direct cortical ICH involvement or progressive small vessel damage related to cerebral amyloid angiopathy [9,10].

Seizures after carotid endarterectomy and angioplasty: Seizures are a rare complication of carotid endarterectomy (0.8%). They are a component of the so called 'hyperperfusion syndrome' that can develop hours or days after surgical relief of long-standing tight carotid stenosis. The vascular pathogenesis of such seizures is not always hyperperfusion; but also due to microembolism, hypoperfusion, or hypertensive encephalopathy [5,11,12].

Moyamoya disease: The 2 cardinal clinical signs of moyamoya disease are ischemic attacks or intracranial hemorrhage. Epilepsy is the third most common manifestation of moyamoya disease. About 20%-30% of cases present with seizures. Recurrent seizure attacks in moyamoya disease should be regarded as symptomatic localization-related epilepsy [5,13].

Transient ischemic attack: Is associated with the lowest incidence of seizures (3.7%) [5,6].5,6

CLINIC

Focal and Generalized Seizures

The clinical diagnosis of early seizures is sometimes easy, especially in cases of clonic manifestations on the side of hemiplegia. However, the symptomatology is more often non-specific, with fluctuating arousal, behavioral change or transient worsening on neurological examination. Ictal and post-ictal confusional states of up to seven to eight days have

been described. Thus, in these cases, diagnosis can be difficult, and it seems standard 20-min Electroencephalography (EEG) is rarely contributory [1,5,11,12].

Gasparini et al. demonstrated that patients with leukoaraiosis frequently exhibit clinical and EEG signs suggestive of temporal lobe epilepsy, but patients with large vessel infarct had signs of frontal lobe epilepsy [2,3,5].

Status Epilepticus (SE) after Stroke (Table 2)

Non Convulsive Status Epilepticus (NCSE) was the predominant SE type in the early onset post-stroke seizure patients (85%) and was as frequent as convulsive status epilepticus (50%) in the late-onset group. In both the acute and chronic situations, NCSE should always be considered in stroke patients in whom there is unexplained change in consciousness and behavior [1,6,13,14]. It is also unclear whether early poststroke status epilepticus is a risk factor for late-onset seizures. Several studies have confirmed that status epilepticus as a presentation does not predict subsequent development of epilepsy [2,16].

ELECTROENCEPHALOGRAM (EEG)

Standard 20-min EEG recordings of the acute phase of stroke usually show non-specific abnormalities, such as slow waves in the side of the infarct (the most frequent finding) and periodic lateralized epileptiform discharges (PLEDs), but otherwise rarely contribute to a positive diagnosis of epileptic seizures. EEG can be normal in about 5% of acute stroke and, therefore, normal EEG result does not rule out epileptogenicity. Nevertheless, EEG is necessary to establish the diagnosis of nonconvulsive status epilepticus, and detect persistent epileptiform activity after an apparently successful treatment of convulsive status epilepticus [1,5,7,12,13].

Periodic Lateralized Epileptic Discharges (PLEDs), often associated with metabolic abnormalities (hyperglycemia, fever) and common abnormalities in the acute phase of severe cerebral ischemia, are considered as an EEG signature of an unstable neurobiological condition that creates an ictal-interictal continuum in a sick brain, that can lead to seizures when any acute derangements coexist. However, PLEDs are considered as a true epileptic phenomenon (subtle status epilepticus) by some authors. Furthermore, PLEDs are more frequently observed in stroke patients with early-onset seizures and are rarely described in cases of late-onset seizures. Aggressive antiepileptic treatment is recommended by some to

enhance recovery, but this attitude is contested by others [4,13,14].

Focal slowing or diffuse slowing activities, rhythmic slow waves are associated with a low risk of early onset seizures whereas focal spikes, sharp waves, periodic lateralized, or periodic bilateral discharges are associated with a higher risk. Frontal Intermittent Rhythmic Delta Activities (FIRDAs) and diffuse slowing can be considered as possible indicators of late-onset seizures [1,5,7,15,16].

RADIOLOGICAL STUDIES

When CT scan is used in conjunction with EEG and clinical findings, it is a useful diagnostic tool to establish the cause of the first seizure in adults [3,4]. However, brain MRI is the imaging modality of choice, as it will show a number of abnormalities that may be missed on CT, for example, cortical malformations, hippocampal sclerosis, small mass lesions, and cavernoma, particularly in the temporal lobes [1,5,9,10]. Arterial Spin-Labeling (ASL), is very useful in early seizure and in the differentiation of late seizure due to simultaneous evaluation of changes to both cerebral perfusion and the primary stroke lesion [1,5,7,13,14].

Late-Onset Epilepsy (LOE) patients have an increased volume of White Matter Lesions (WML) and lower cortical volumes, which is recognized to reflect cerebral small vessel disease in the absence of another disease process. Seizures may also prompt a vicious cycle, whereby areas of cerebrovascular damage continue to be disrupted by further seizure [1,8,11,16].

DIFFERENTIAL DIAGNOSES

1. In the context of recent stroke, metabolic and toxic disorders are causes of fluctuations in arousal and movement disorders, which should not be confused with epileptic clonic seizures. In such cases, EEG recordings are essential for making the diagnosis and avoiding the unnecessary addition of an antiepileptic drug that can worsen encephalopathy [1,7,8,14,17].

2. Limb tremor is clinically manifested by tremor mimicking myoclonia, but manifesting exclusively on standing, caused by transient hemodynamic ischemia observed in cases of tight stenosis of the internal carotid artery or, less frequently, the intracranial vessels.

3. Midbrain strokes or acute insults of the subthalamic nuclei, whether ischemic or hemorrhagic, can provoke abnormal movements that mimic epileptic movements.

TREATMENT

Who Should be Treated?

Except for cerebral venous thrombosis, Antiepileptic Drugs (AEDs) are used after a second acute seizure, a prolonged first acute seizure or status epilepticus. Other neurologists, start AEDs after a first acute seizure, after excluding other causes for the seizures, based on the risk of status epilepticus and on the increased risk of remote seizures [1,4,11]. A first unprovoked late-onset seizure, is indicative of antiepileptic medication [2,6,17].

The Choice of Adequate Treatment

Criteria for helping to select the most appropriate AED include: (1) efficacy; (2) tolerability in population who are often elderly and have comorbidities; (3) hepatic and renal function; (4) interactions between AEDs, and with other drugs (antithrombotic medications*); (5) cost and availability, and patient's preferences (6) [3,8,1,4,14]. Treatment options should be extrapolated from those of epilepsy in general. Classic AEDs (phenytoin 100-300 mg/day, carbamazepine 400-1600 mg/day or valproic acid 500-2500 mg/day) are the first treatment options. They have poor safety profile; important drug interactions and adverse effects (negative cognitive effects, deleterious effects on neurological recovery). In cases of stroke associated with atheroma, it is necessary to be aware of classic antiepileptic drug-induced dyslipidemia. Carbamazepine is preferable in partial epilepsies. The new AEDs (lamotrigine 100-200 mg/day; gabapentine 900-3600 mg/day; levetiracetam 1000-3000 mg/day; topiramate 200-400 mg/day; zonisamide; oxcarbazepine and tiagabine) should be reserved for those patients who do not tolerate classic AEDs or in treatment failures with the classic AEDs [1,5,8,11,12, 16-18]. They have good safety profile and less drug interactions than classic AEDs and may be preferable for patients taking several other medications, as is usually the case in stroke survivors. They can also be used in monotherapy or as add-on treatments. There is evidence regarding their efficacy as an add-on treatment for drug-resistant partial epilepsy [5,6].

New AEDs should be the first option in patients who need prolonged oral anticoagulation for secondary stroke prevention [5,6]. Vascular epilepsy is usually easy to treat with monotherapy, as 80% of patients are seizure-free after 1 year [2,14].

Treatment Principles

An important principle of antiepileptic treatment in the elderly is to 'start low, go slow' [6,13]. Individualized evaluation of risk-benefit balance of antiepileptic medication: risk of seizures and the high probability of adverse effects due to high susceptibility of this population, some of which may be disabling; (e.g. somnolence, gait imbalance and ataxia, confusion, mental slowing, weight gain or loss of appetite and weight loss, and liver toxicity; and cognitive impairment). If the residual deficit can be attributed to ischemia and not only postictal deficit, then seizures are no longer a contraindication for intravenous thrombolysis [4,16,17]. To be careful in the use of some drugs in stroke patients, this can decrease seizure threshold [1,7,12].

How Long Should Antiepileptic Treatment be Maintained?

It is recommended to stop medication once the acute stage is over or at the first post-stroke, 3-month visit after an early post-stroke seizure, because, early seizures are not predictive of later vascular epilepsy [1,6,13,17]. For remote seizures, a seizure-free period of 2-3 years before a trial of AED withdrawal is recommended. Other neurologists start AED reduction after a seizure-free period of 6-12 months [1,2,11,12].

Management of Status Epilepticus

Intravenous (IV) diazepam or IV lorazepam is used as a first option, followed by IV phenytoin or fosphenytoin if seizures recur, and barbiturate if seizures are not controlled. IV valproic acid is an alternative in patients with contraindications to phenytoin and fosphenytoin [1,3,6,14]. For 'subtle status epilepticus' (synonym: Myoclonic Status Epilepticus in Coma) some neurologist administer high dose intravenous AED therapy (barbiturate, valproate, or levetiracetam) for 12 h only, to be discontinued if there is no improvement [1,5,11].

Guidelines of the French Neurovascular Society (SFNV)

To use only drugs with demonstrable efficacy in focal epilepsies, such as carbamazepine, oxcarbazepine, lamotrigine and levetiracetam. For the elderly patients, it is recommended

to preferentially use lamotrigine, gabapentin, lacosamide and zonisamide [1,6,11].

European and North American Guidelines

“Standard IV and oral antiepileptic drugs are in general used (level of evidence: III) [6].

For ischemic stroke, there is no evidence that prophylactic anticonvulsive treatment is beneficial (level of evidence: IV)” [2,6]. For intracerebral hemorrhage, it is recommended that “seizure activity must be treated aggressively (level of evidence: V). Prophylactic antiepileptic therapy (preferably phenytoin) may be considered for a month and then tapered and discontinued if no seizure activity occurs during treatment” [8].

PROGNOSIS

Mortality

Early onset of seizures after stroke is often associated with a higher mortality rate than late-onset seizures. The increased mortality may be due both to the severity of the underlying stroke and also the synergistic effect of combined injuries from seizures and cerebral vascular ischemia [8,11]. The immediate prognosis of status epilepticus is poor, in particular if of early-onset, with an increased mortality and higher morbidity [10,13].

Morbidity

The occurrence of epilepsy in a patient with stroke significantly increases infarct size leading to an irreversible state of injury and will often further inhibit recovery and decrease quality of life, an effect that can be ameliorated with the administration of certain neuroprotective agents. Indeed, the seizures, even if infrequent, may result in dependency, increased social restriction, neurological deficit and psychological disability (depression and anxiety which can prove a hurdle in rehabilitation). These effects may be the direct biological consequence of the seizures on the ischemic brain or secondary psychosocial effects [1,14,17-19].

CONCLUSION

Post-stroke seizures and epilepsy imposes a clinical dilemma in terms of diagnosis, and its management is controversial. Randomized controlled trials of AED prophylaxis for acute and remote seizures are essential to improve the evidence level of current guidelines and recommendations for the management of post-stroke seizures.

Competing Interests

The authors report no conflicts of interest.

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