29th Annual Meeting “Epilepsy across the lifespan”

1st August 2025: 13.45-14.15

Stroke-Related Epilepsy in Adults and Elderly: Prevention and Treatment

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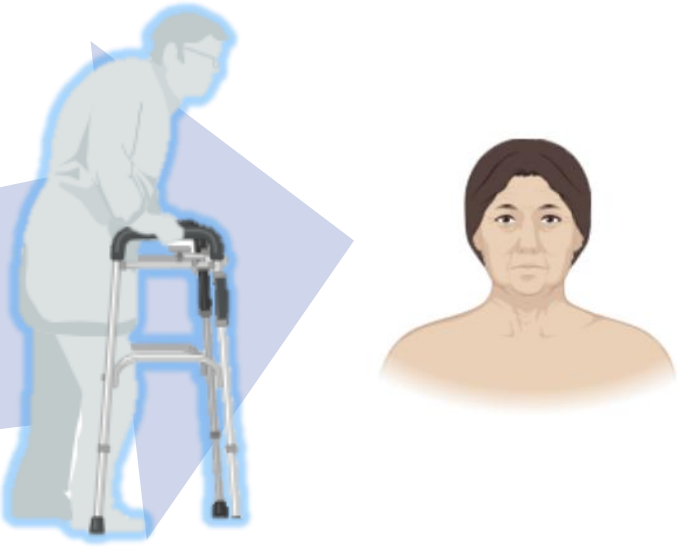
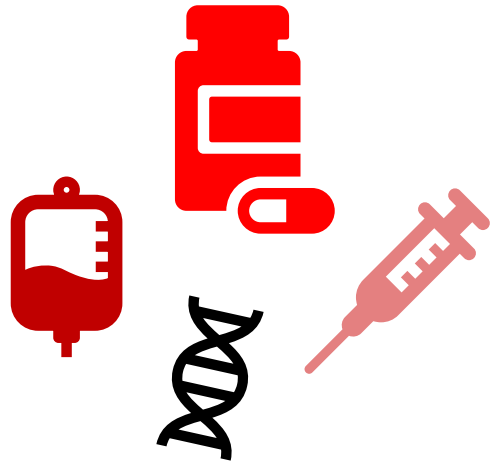
Cerebrovascular disease, craniocerebral trauma, intracranial infection and metabolic abnormality are common causes of seizures and epilepsy in adults





Outlines

- Introduction : The importance of seizure control
- Definition and diagnosis of post-stroke seizure and epilepsy
- Pathogenesis of seizures and epilepsy after stroke
- Management and treatment
- Prevention
- Future direction

EUROPEAN STROKE JOURNAL
ILAE International League Against Epilepsy

"**Stroke** is the most common cause of epilepsy in older age. **Subclinical cerebrovascular disease** is believed to underlie some of the **30-50%** of **late-onset epilepsy** without a known cause."

Li et al. *Epilepsia*. 1997; 38:1216.

Cleary et al. *Lancet.* 2004; 363:1184.

Etiologies of Status Epilepticus

- **Known (Symptomatic)**
  - Acute
    stroke, intoxication, encephalitis etc.
  - Remote
    posttraumatic, postencephalitic, poststroke etc.
  - Progressive
    brain tumor, dementia, genetic epilepsy etc.
  - SE in defined electroclinical syndrome
- **Unknown (cryptogenic)**
- **AEDs withdrawal in epilepsy patient**

	Frequency (%)	Mortality (%)
Acute		
Stroke	22%	33%
Metabolic abnormalities	15%	30%
Hypoxia	13%	53%
Systemic infection	7%	10%
Anoxia	5%	71%
Trauma	3%	25%
Drug overdose	3%	25%
CNS infection	3%	0%
CNS haemorrhage	1%	0%
Chronic		
Low concentration of anti-epileptic drugs	34%	4%
Remote symptomatic (eg, tumour, stroke, trauma)	25%	14%
Alcohol misuse	13%	20%
Tumour	7%	30%
Idiopathic	3%	25%

Some patients had more than one aetiology.

Table 1: **The frequency and mortality associated with acute and chronic causes of status epilepticus in adults[20]**

Eugen Trinka et al. *Epilepsia*. 2015; 56(10):1515–1523.

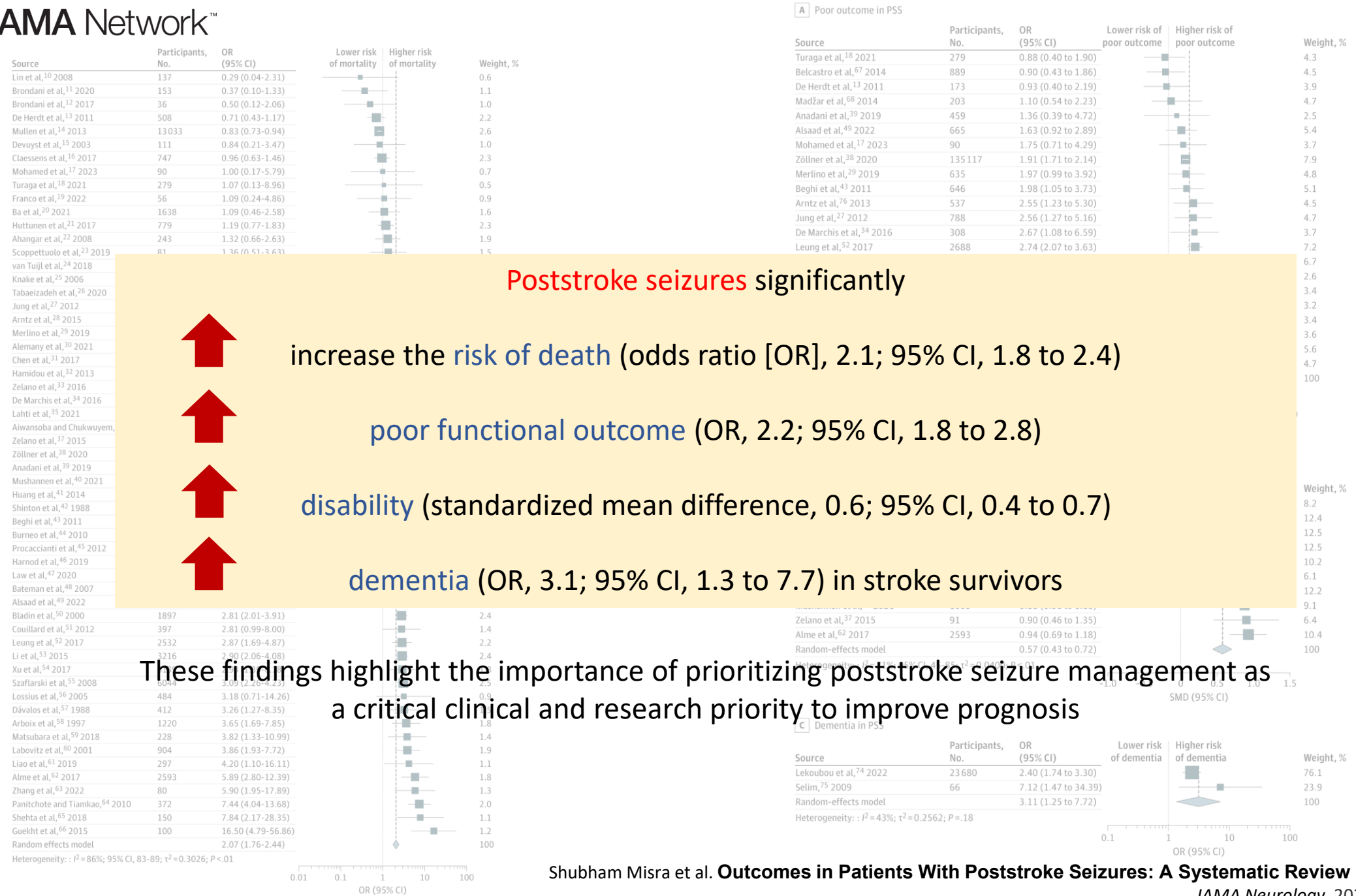
Betjemann, John P et al. *The Lancet Neurology. 2015;* 14(6): 615 – 624.

Importance of Seizure Control for Prognosis

- From population-based study, *Neurology* 1996 - in the first year after stroke, the risk of epilepsy is about **23 times** higher than that in the general population
- The analysis further indicated that people experiencing early seizures, regardless of whether the stroke was ischemic or hemorrhagic, faced an increased risk of death
- Both early and late seizures were linked to poorer functional outcomes across stroke subtypes
- Data on seizure frequency and their association with mortality or functional outcomes were unavailable

Ren Z et al. *Clinical Neurology and Neurosurgery*. 2022;220:107362.
Shubham Misra et al. *JAMA Neurology.* 2023;80;(11):1155-1165.

JAMA Network™



Poststroke seizures significantly

↑ increase the risk of death (odds ratio [OR], 2.1; 95% CI, 1.8 to 2.4)

↑ poor functional outcome (OR, 2.2; 95% CI, 1.8 to 2.8)

↑ disability (standardized mean difference, 0.6; 95% CI, 0.4 to 0.7)

↑ dementia (OR, 3.1; 95% CI, 1.3 to 7.7) in stroke survivors

These findings highlight the importance of prioritizing poststroke seizure management as a critical clinical and research priority to improve prognosis

Shubham Misra et al. **Outcomes in Patients With Poststroke Seizures: A Systematic Review and Meta-Analysis.** *JAMA Neurology.* 2023;80;(11):1155-1165.

Original research article

EUROPEAN STROKE JOURNAL

European Stroke Journal
2016, Vol. 1(4) 272–278

DOI: 10.1177/2396987316669000
eso.sagepub.com
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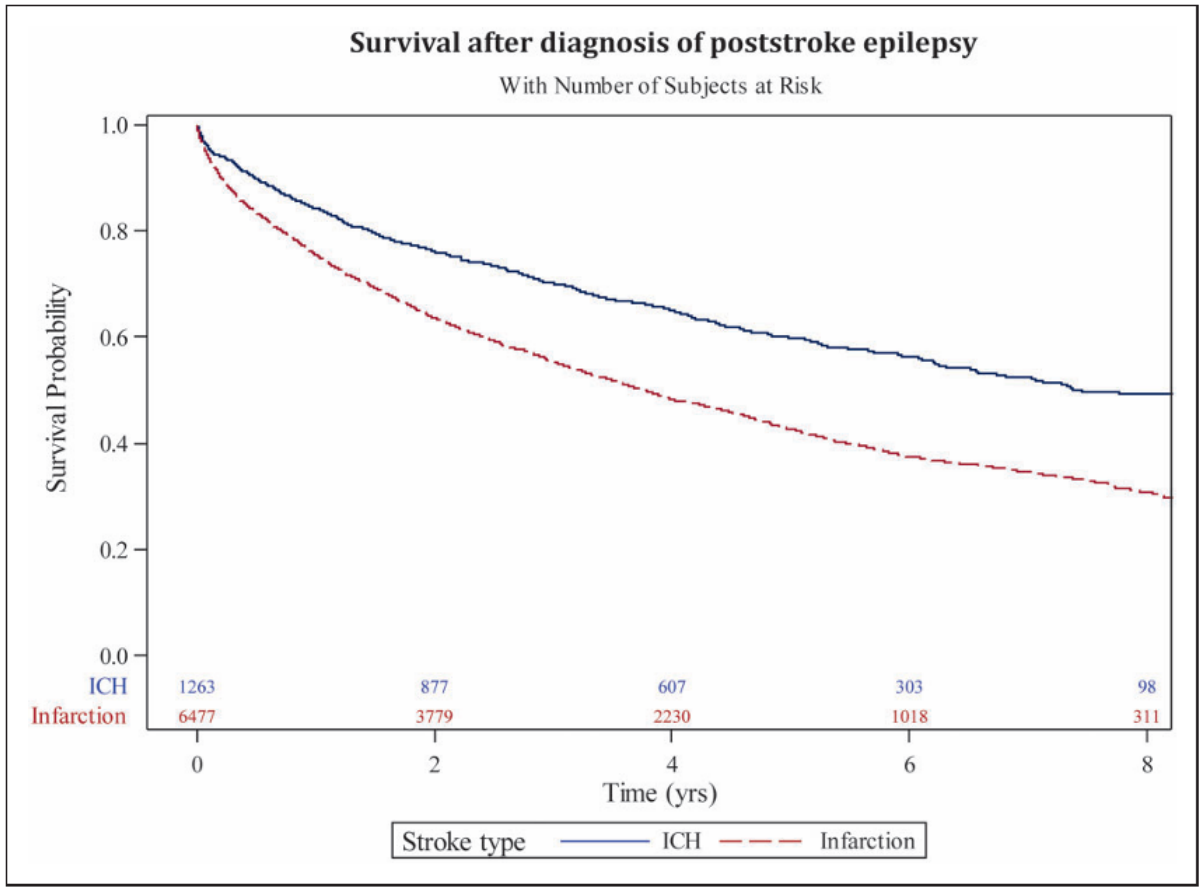
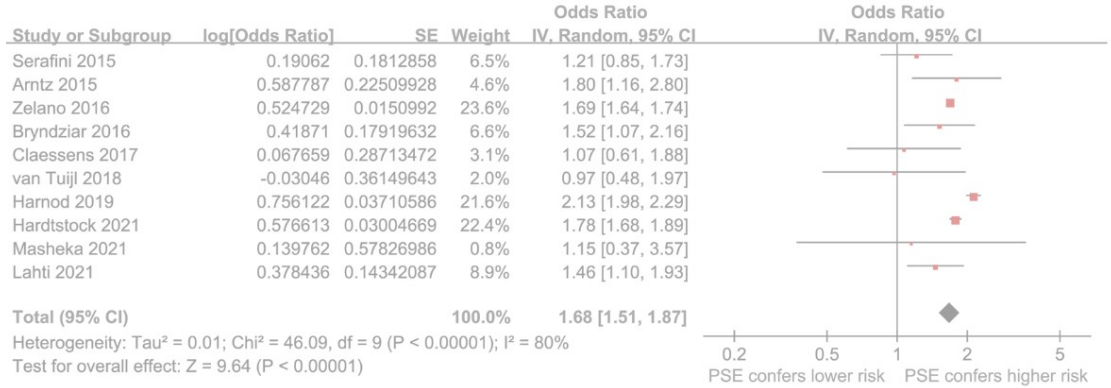
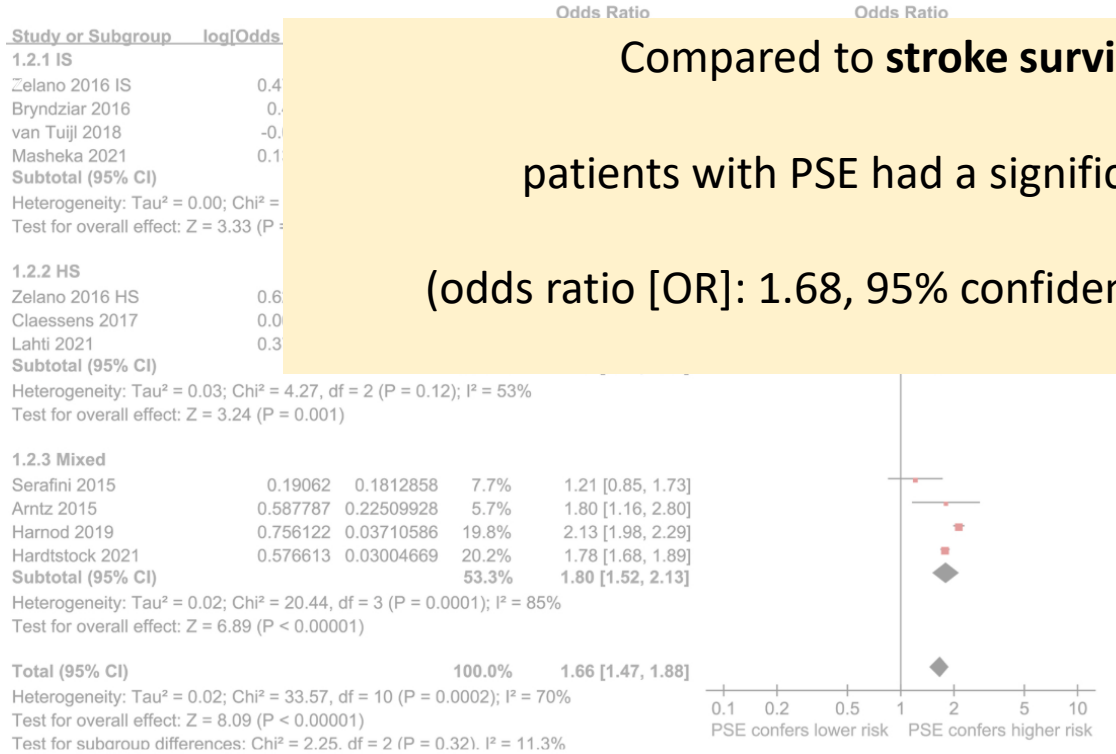
Association between poststroke epilepsy and death: A nationwide cohort study

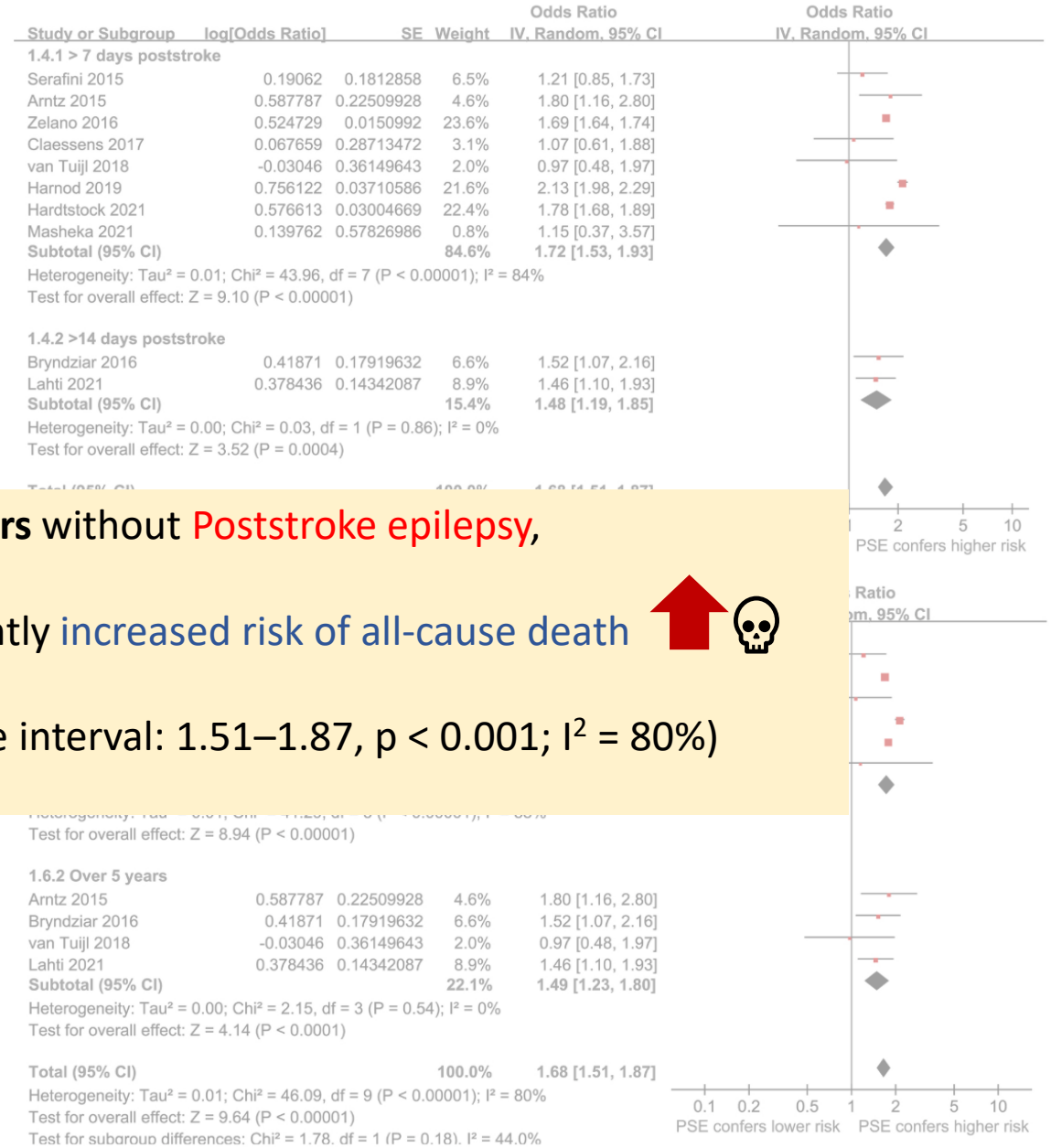
Johan Zelano[1,2], Petra Redfors[1,2], Signild Åsberg[3,*] and Eva Kumlien[4,*]

- In 106,455 patients, PSE was detected in 7.3%, with lower cumulative incidence after ischemic stroke (6.4%) than after intracerebral haemorrhage (12.4%)
- Stroke severity, intracerebral haemorrhage and young age were associated with a risk of PSE
- **The risk of death was increased in patients with PSE** (hazard ratio: 1.68, 95% confidence interval: 1.25–1.53)
- Also, with adjustments for age, comorbidities and stroke severity, an increased risk of death associated with PSE remained









Compared to **stroke survivors** without Poststroke epilepsy,

patients with PSE had a significantly increased risk of all-cause death

(odds ratio [OR]: 1.68, 95% confidence interval: 1.51–1.87, $p < 0.001$; $I^2 = 80\%$)

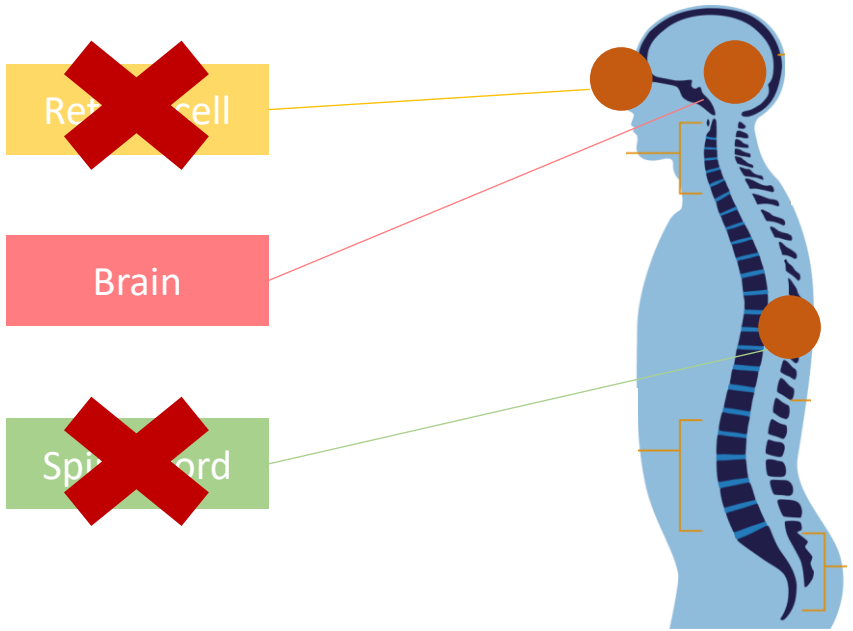
Ren Z et. al. **Post-stroke epilepsy and risk of all-cause mortality: A systematic review and meta-analysis of cohort studies.** *Clinical Neurology and Neurosurgery.* 2022;220:107362.

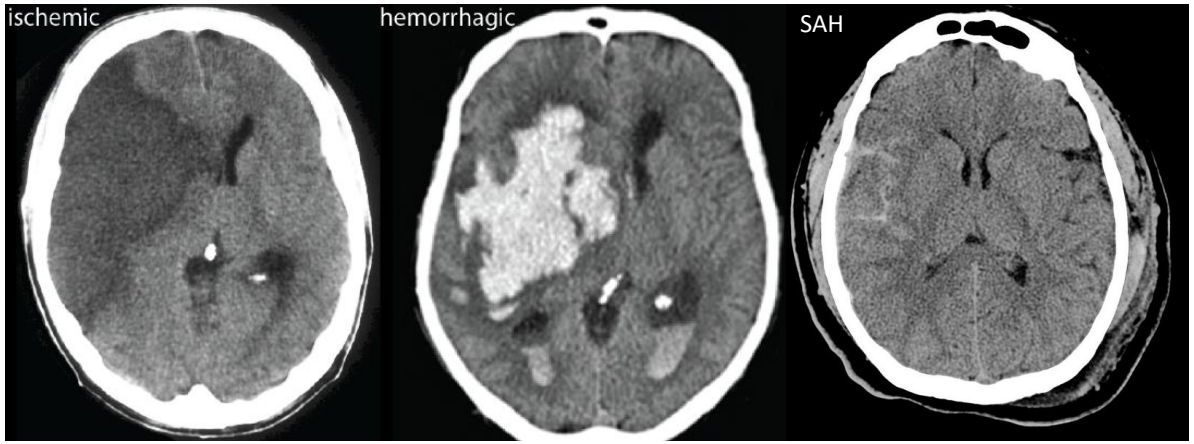
Stroke

definition

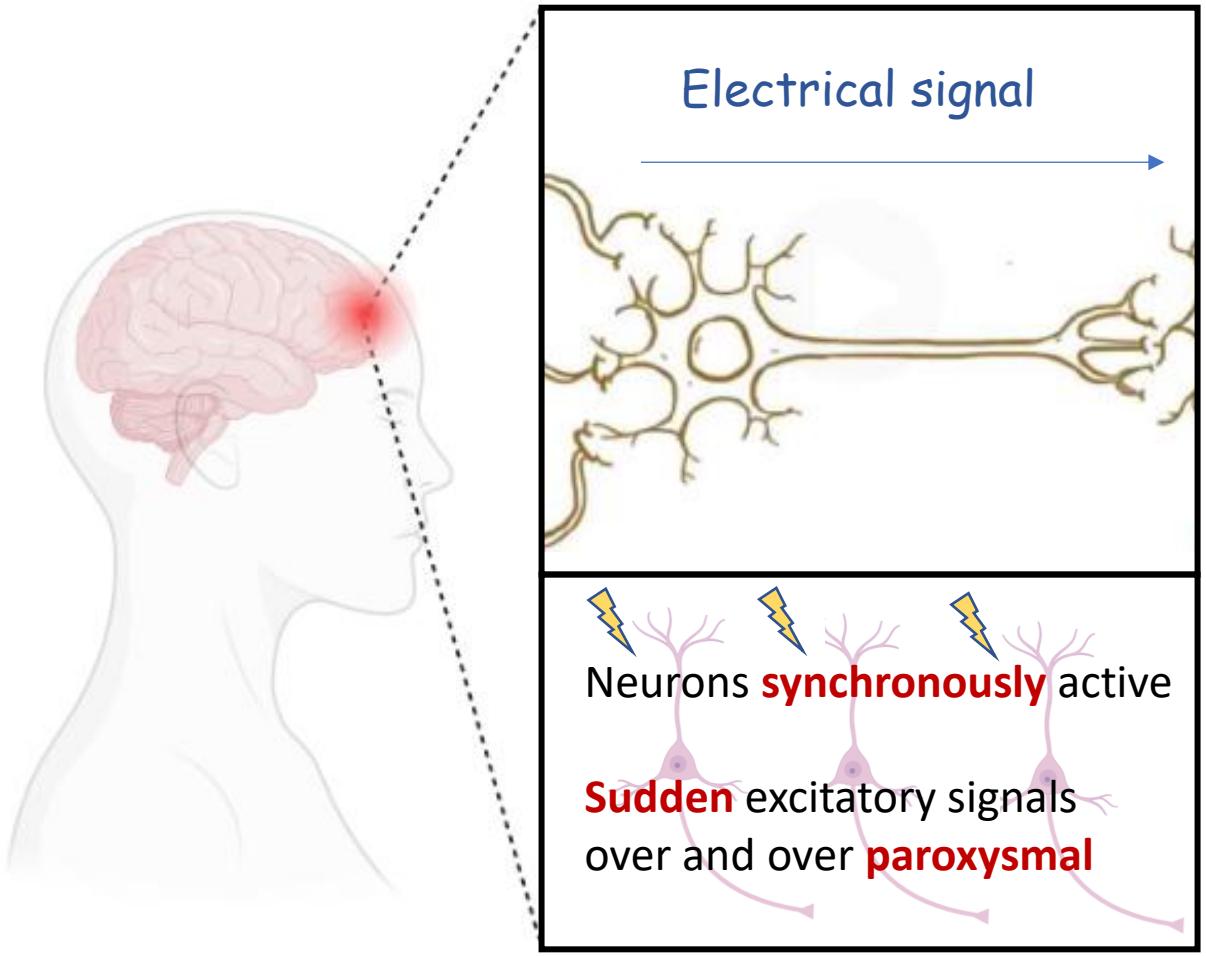
Diagnosis of stroke = Acute focal injury of CNS + Vascular cause + Acute/sudden or awakening onset

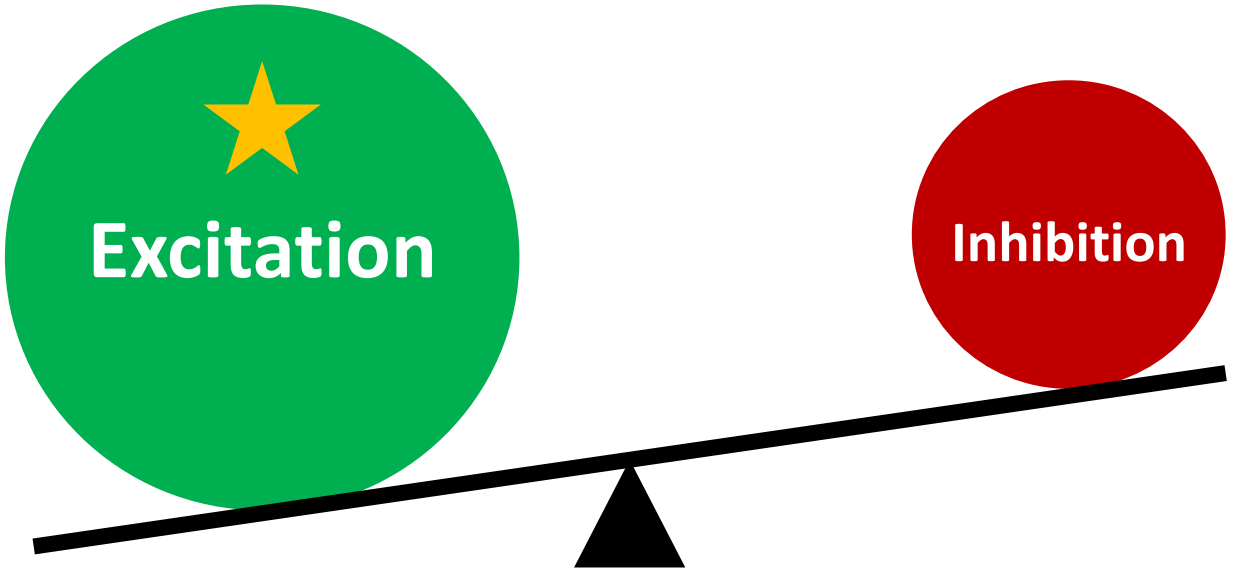
Cerebral infarction	Intracerebral hemorrhage	Subarachnoid hemorrhage





Pathophysiology of seizure





Definition of seizure and epilepsy

- **An epileptic seizure** is a transient occurrence of signs and/or symptoms due to abnormal excessive or synchronous neuronal activity in the brain

- **Epilepsy** is a disorder of the brain characterized by an enduring predisposition to generate epileptic seizures

✓At least 2 unprovoked (or reflex) seizures occurring > 24 hours apart

✓One unprovoked (or reflex) seizure and a probability of further seizures > 60% occurring over the next 10 years

✓Diagnosis of epilepsy syndrome

Fisher, R. S., et al. *Epilepsia*. 2005; *46*(4), 470–472.

Epilepsia, 51(4):671–675, 2010
doi: 10.1111/j.1528-1167.2009.02285.x

SPECIAL REPORT

Recommendation for a definition of acute symptomatic seizure

*[I]Ettore Beghi, †Arturo Carpio, ‡Lars Forsgren, §Dale C. Hesdorffer, ¶Kristina Malmgren, #Josemir W. Sander, **Torbjorn Tomson, and §W. Allen Hauser

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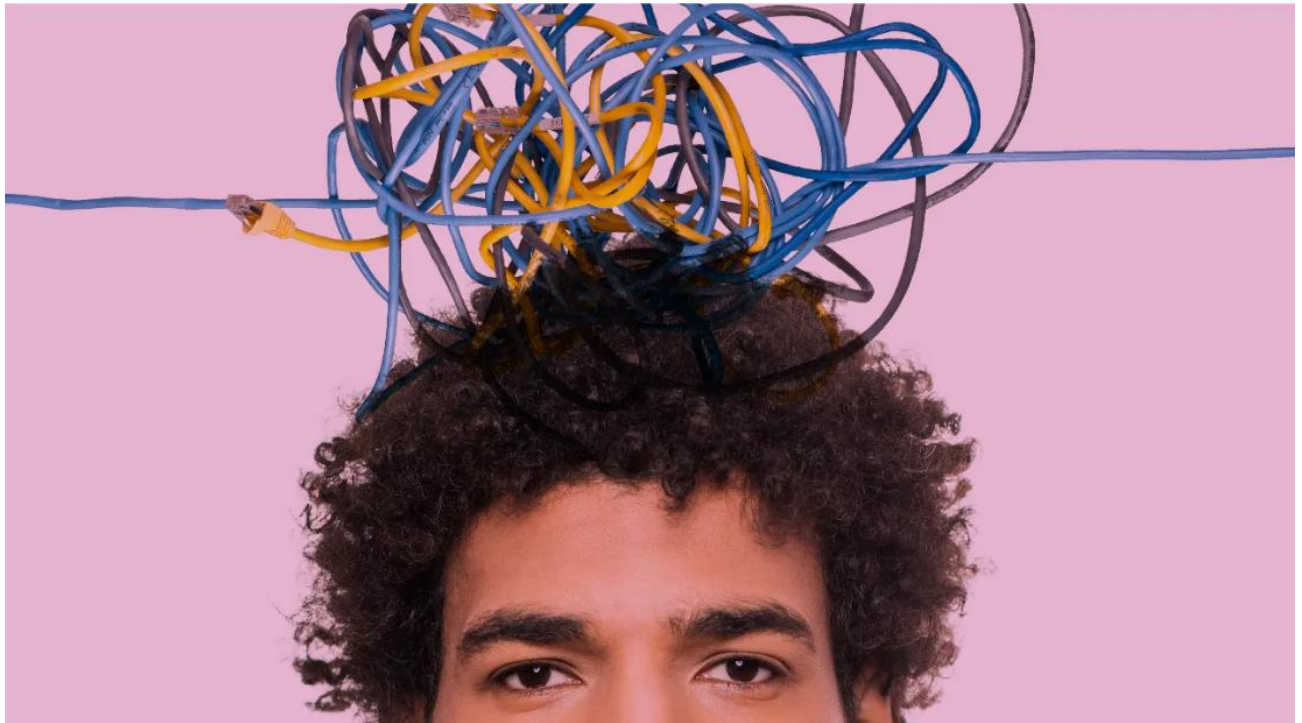
An acute symptomatic seizure is defined as a clinical seizure occurring at the time of a systemic insult or in close temporal association with a documented brain insult. Suggestions are made to define **acute symptomatic seizures as those events occurring within 1 week of stroke**, traumatic brain injury, anoxic encephalopathy, or intracranial surgery; at first identification of subdural hematoma; at the presence of an active central nervous system (CNS) infection; or during an active phase of multiple sclerosis or other autoimmune diseases.

Glossary terms

- Acute symptomatic seizure
- Late poststroke seizure =
- Poststroke Epilepsy (PSE)?



Definitions of terms

Tissue-based approach

Ideal

Time-based approach

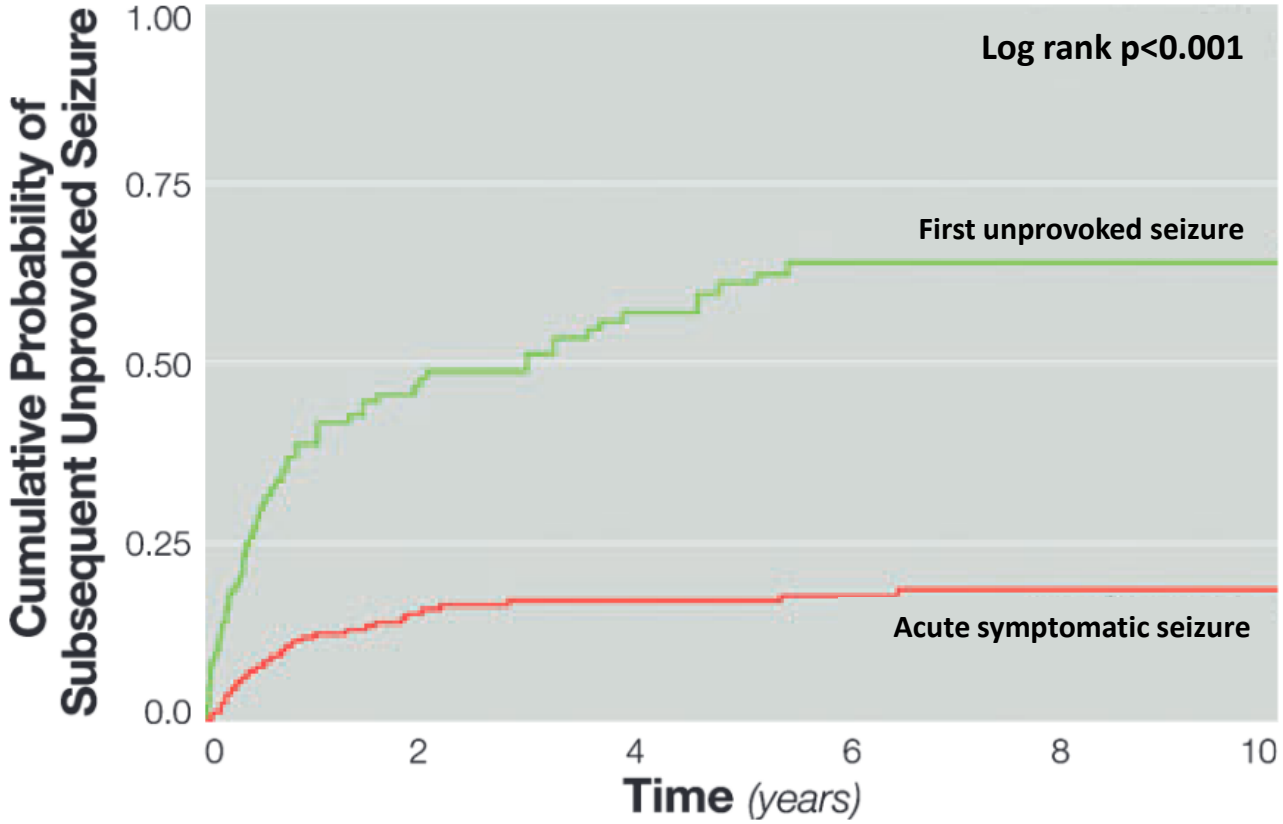
Poststroke seizure

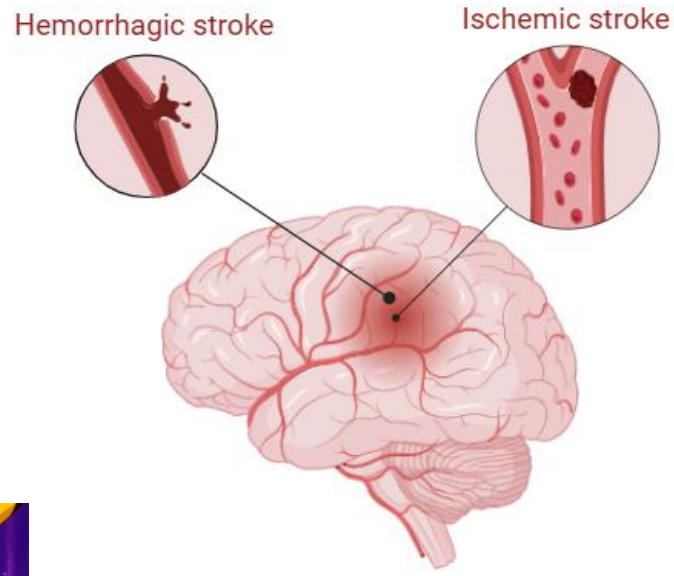
Within 3-7 days
Termed as early seizure

Poststroke epilepsy (PSE)

After 7 days
Termed as late seizure

ILAE International League Against Epilepsy



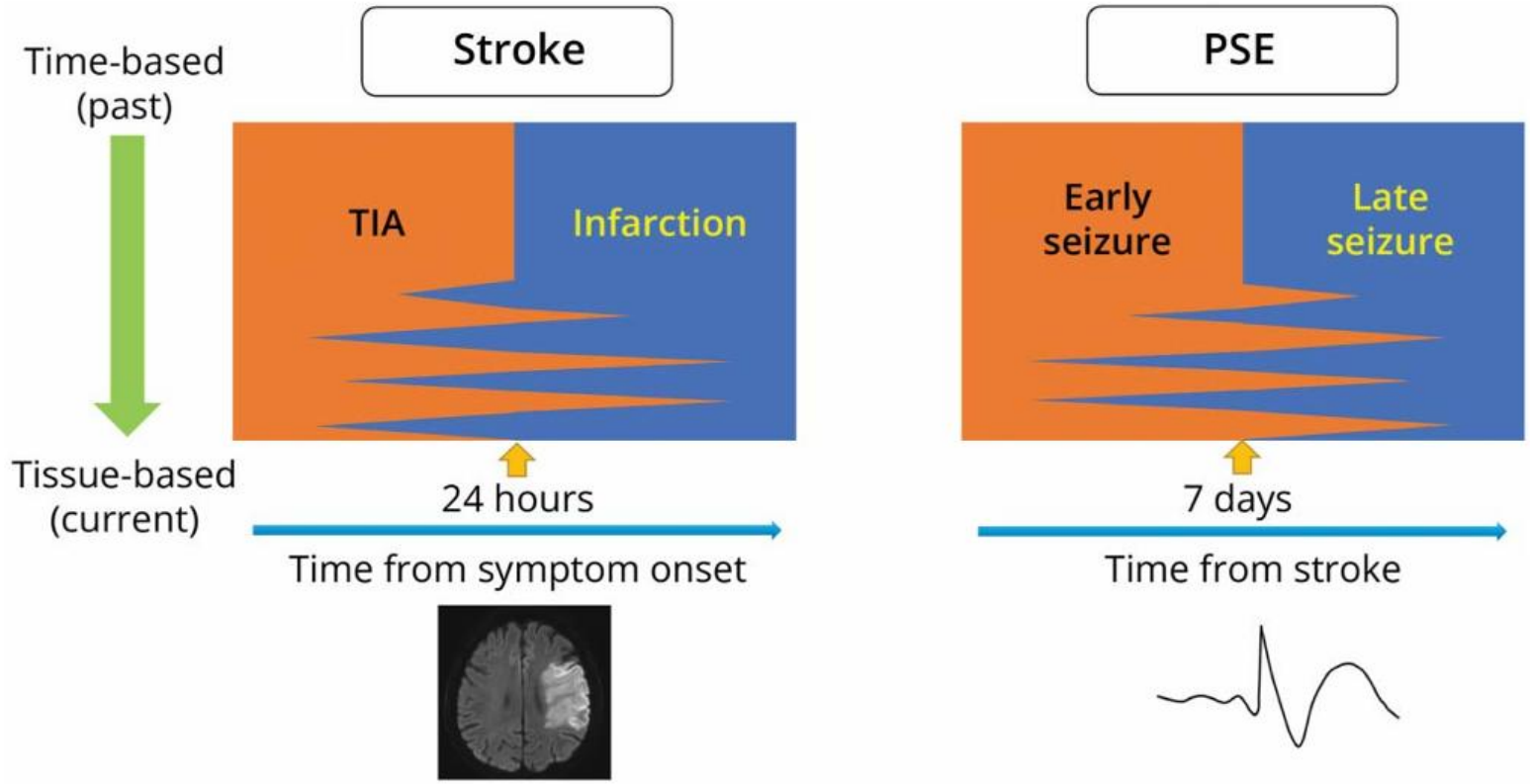


Poststroke epilepsy

	Acute symptomatic seizure	First unprovoked seizure
Stroke	33.0% (95% CI = 20.7–49.9%)	71.5% (95% CI = 59.7–81.9%,p = 0.001)
Traumatic brain injury	13.4% (95% CI = 7.0–24.8%)	46.6% (95%CI = 30.4–66.3%, p < 0.001)
CNS infection	16.6% (95%CI = 9.5–28.0%)	63.5% (95% CI = 21.2–98.6%,p = 0.010)

Hesdorffer, DC, et al. *Epilepsia. 2009;* 50(5):1102–1108.

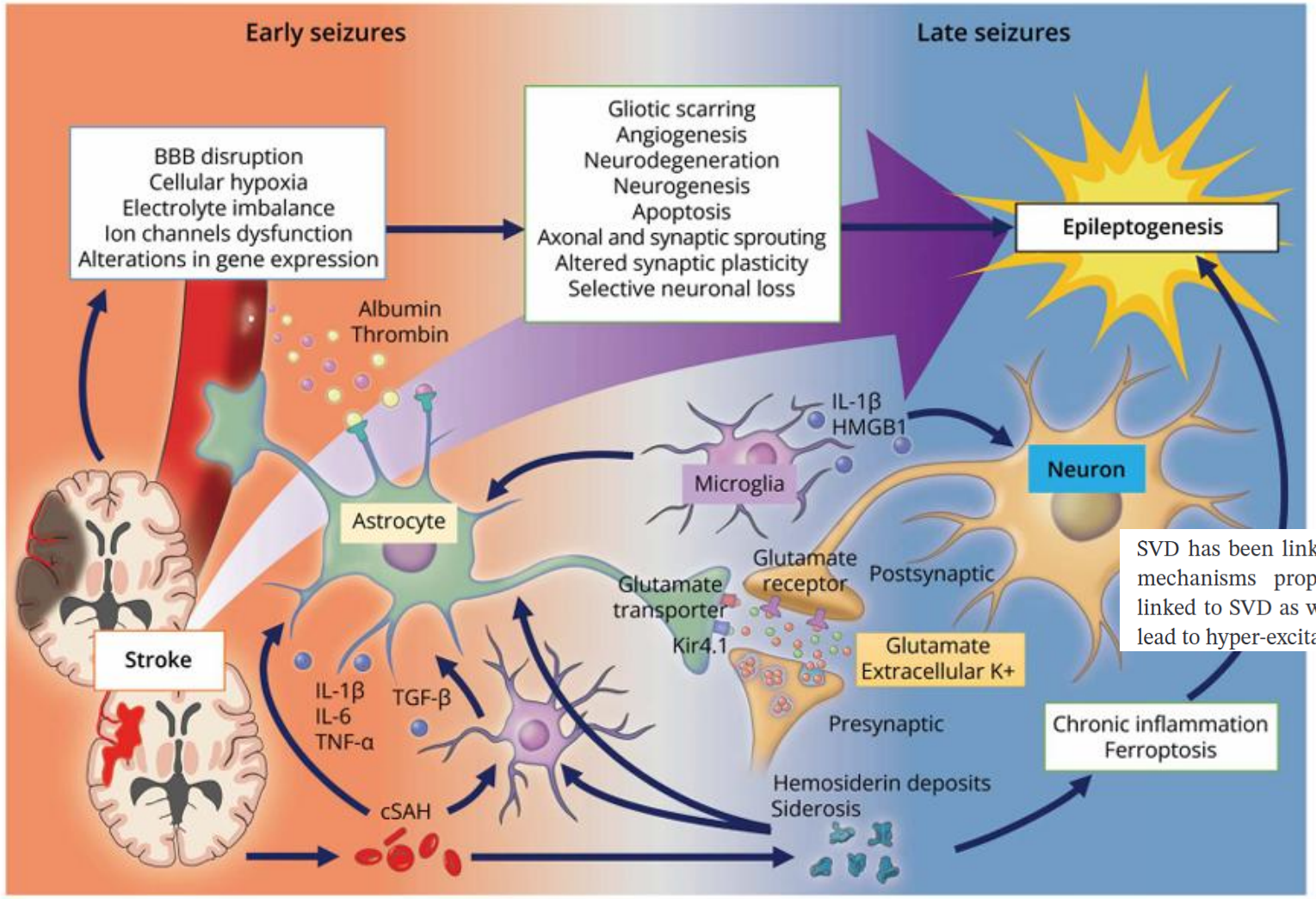
Early and Late Seizures
Shifting From a Time-Based to a Tissue-Based Approach



Identifying epileptogenesis is crucial for selecting the most appropriate treatment strategy for PSE

Tomotaka et al. *Neurology.* 2024; 102:e209450.

Proposed Mechanisms of Acquisition of Epileptogenesis After Stroke



SVD has been linked to temporal lobe epilepsy, and the mechanisms proposed include cortical microinfarcts linked to SVD as well as disruption of U fibers that may lead to hyper-excitability.[24]

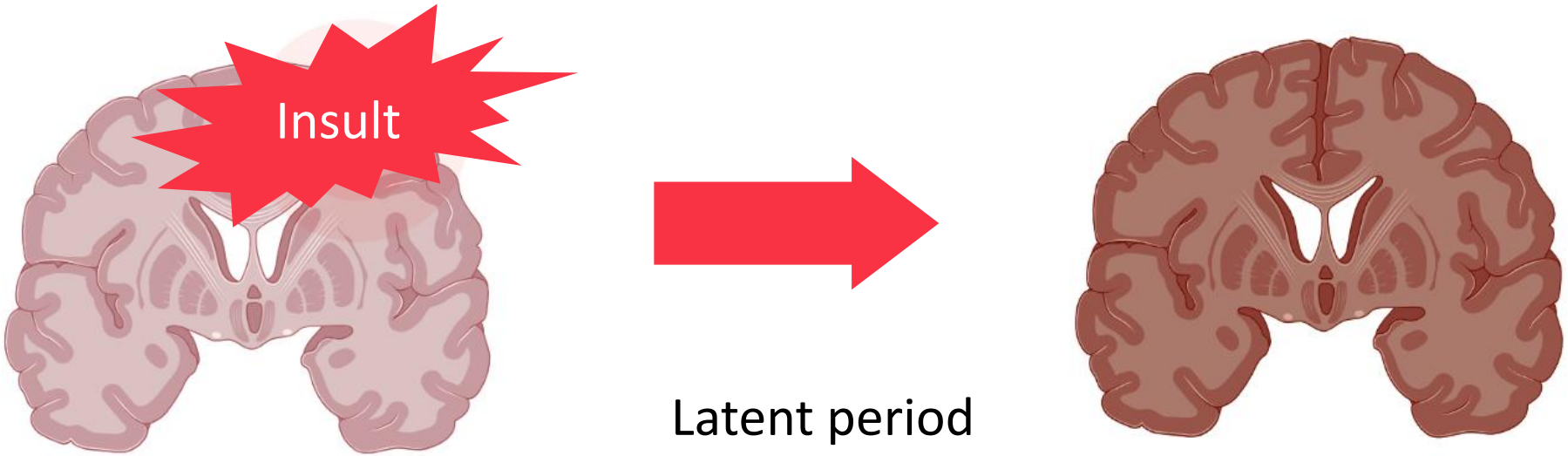
An illustration of epileptogenesis following stroke. Initially, stroke causes BBB disruption, cellular hypoxia, electrolyte imbalance, hemorrhagic transformation, and ion channel dysfunction, leading to early seizures. Subsequently, epileptogenesis can be acquired through secondary changes, such as gliotic 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.

Tomotaka et al. *Neurology.* 2024; 102:e209450.

Epileptogenesis

Normal brain

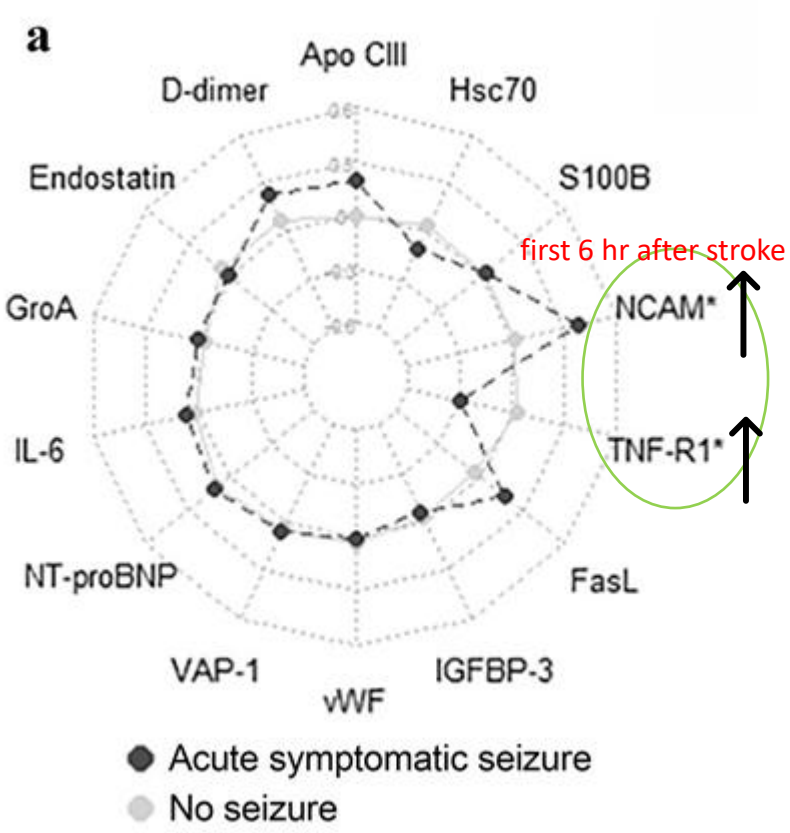
Epileptic brain

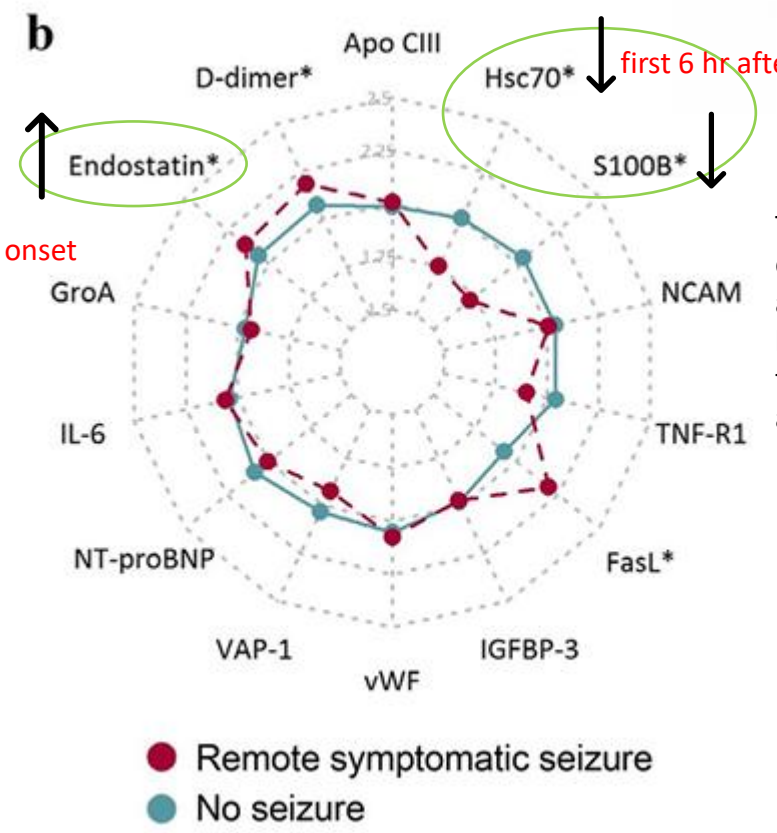


Although early and late seizures should ideally be distinguished based on pathophysiologic differences, not arbitrary time, a tissue-based diagnosis is currently unavailable due to the lack of a validated test or biomarker of epileptogenesis.

Blood and genetic biomarker

TNF-R1 is a proinflammatory cytokine that may exhibit a proconvulsive effect.
Lower levels of TNF-R1 in the blood of patients with acute symptomatic seizures could point towards increased binding of these receptors to TNFα during stroke-induced neuroinflammation.





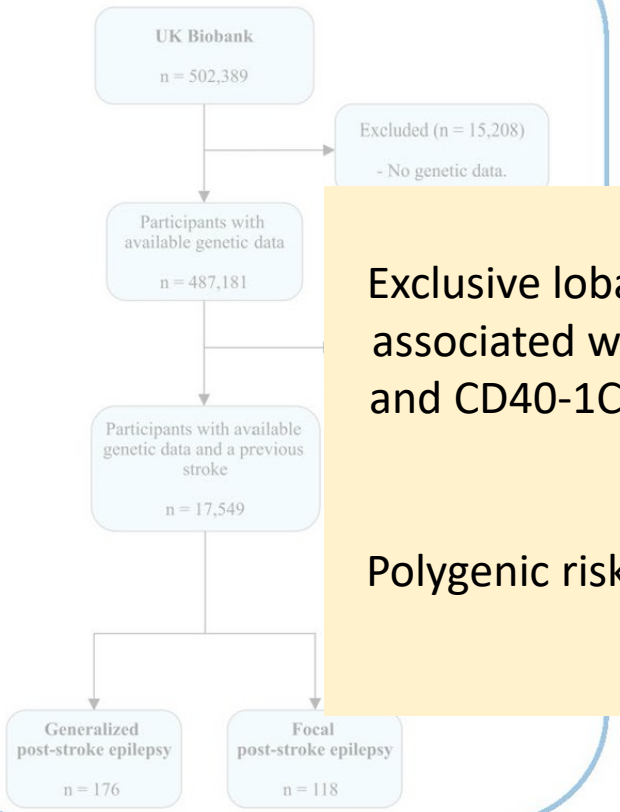
The incidence of post-stroke epilepsy was 17% in cases with abnormalities in all three biomarkers, compared with less than 1% in those with no biomarker abnormalities.

higher neural cell adhesion molecule (NCAM) and lower tumour necrosis factor receptor 1 (TNF-R1) levels

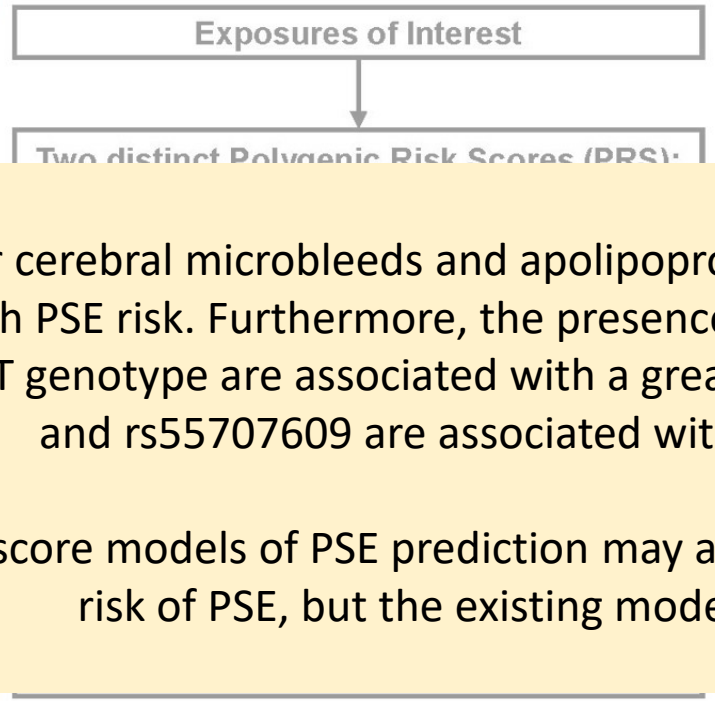
Polygenic Risk of Epilepsy and Post-Stroke Epilepsy

Background:
Epilepsy is highly heritable, with numerous known genetic risk loci. However, the genetic predisposition's role in post-stroke epilepsy (PSE) remains understudied.

Participants



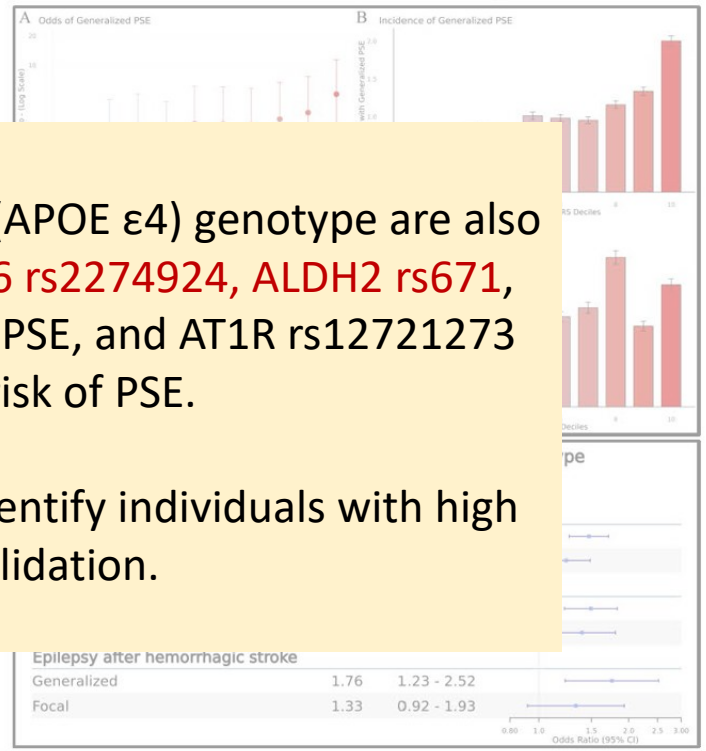
Analytical Framework



Participants with highest PRS decile

5-fold higher odds of Generalized PSE

3-fold higher odds of Focal PSE



Exclusive lobar cerebral microbleeds and apolipoprotein E ε4 (APOE ε4) genotype are also associated with PSE risk. Furthermore, the presence of TRMP6 rs2274924, ALDH2 rs671, and CD40-1C/T genotype are associated with a greater risk of PSE, and AT1R rs12721273 and rs55707609 are associated with a lower risk of PSE.

Polygenic risk score models of PSE prediction may also help identify individuals with high risk of PSE, but the existing model needs validation.

Conclusion:
Genetic predisposition plays an essential role in PSE. PRS is a promising tool for predicting PSE risk.

Santiago Clocchiatti-Tuozzo et. Al. *Stroke*. 2024;55:2835–2843.

Risk factors

- **Young age at stroke**
- **The subtypes of strokes**
  - Cerebral infarction, hemorrhagic transformation, intracerebral hemorrhage, subarachnoid hemorrhage, or TIA
  - Stroke severity (NIHSS >15)
- **Locations of cortical lesions**
  - Frontal, Temporal, Parietal, or Occipital lobes (esp. Middle cerebral artery territory (MCA)) > Infratentorial area
- Lesion size in the major axis (categorized as <15, 15–30, or >30 mm) confirmed by brain imaging
  - Large stroke volume (lesion size scoring model is >10 ml; ≥ 70 ml increases the odds of seizures by fourfold)
- **History of early seizure**
  - Clinical signs and symptoms, EEG findings
- **Blood and genetic biomarker**

Arntz M Renate et.al. *Stroke*. 2015;46: 2309-2311.

Galovic et al. *Drugs & Aging*. 2021; 38:285–299.

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

Scoring Models for PSE

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.

Scoring Models for PSE

Ischemic and hemorrhagic stroke

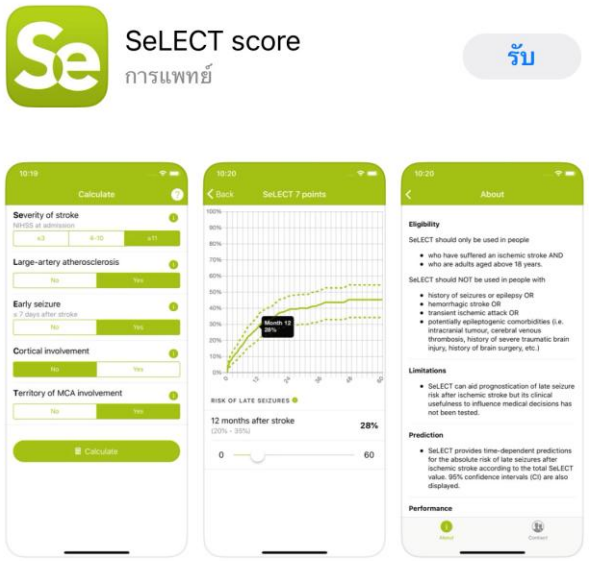
- PoSERS[16]

Ischemic stroke

- PSEiCARe[1]
- SeLECT[13]
- SeLECT-S[33]
- SeLECT 2.0[50]

Hemorrhagic stroke

- CAVE[43]
- CAVS[45]
- LANE[44]
- CAVE-S[33]



for stratified prediction of LS risk

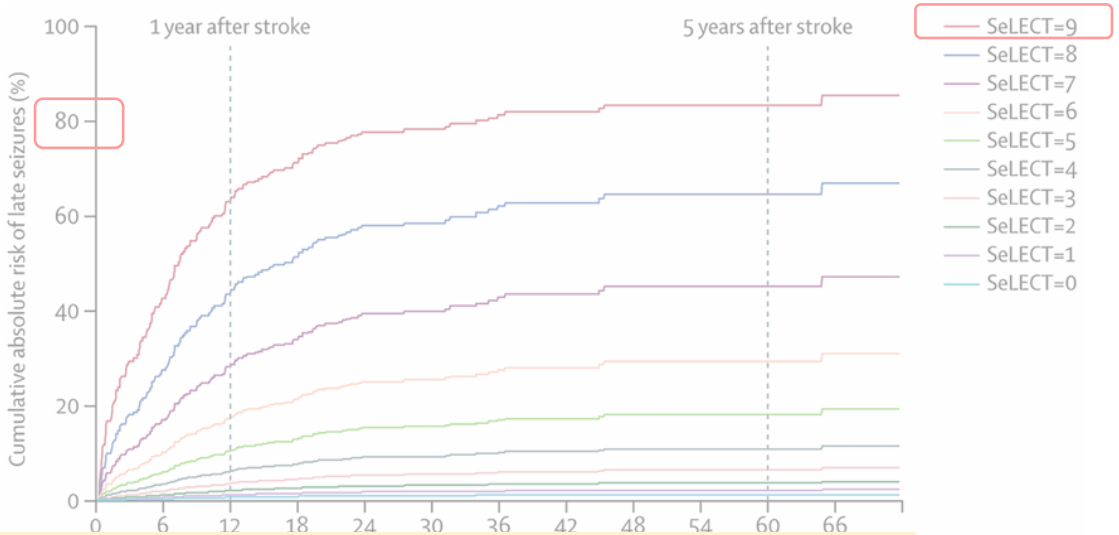
a Calculation of CAVE score

	Points
Cortical involvement	
No	0
Yes	1
Age	
≥ 65 years	0
< 65 years	1
Haemorrhage volume	
≤ 10 mL	0
> 10 mL	1
Acute symptomatic seizure	
No	0
Yes	1

b Risk of remote symptomatic seizures

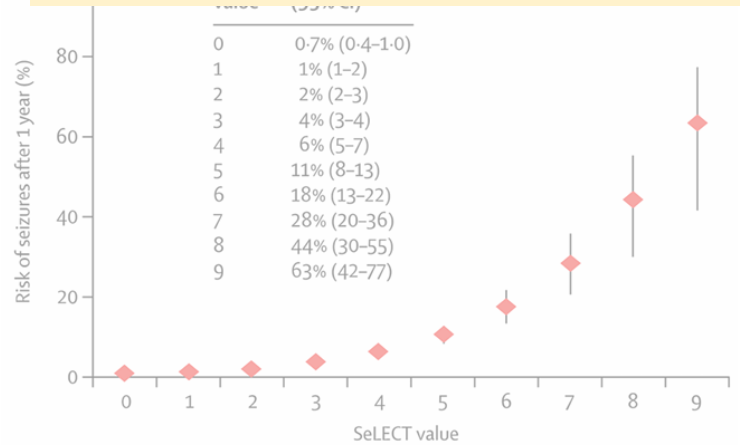
CAVE score	Seizure risk	
	Derivation	Validation
0 points	0.6%	3.1%
1 point	3.6%	5.0%
2 points	9.8%	15.8%
3 points	34.8%	13.5%
4 points	46.2%	37.5%

	SeLECT score (points)
(Se) Severity of stroke	
NIHSS ≤3	0
NIHSS 4–10	1
NIHSS ≥11	2
(L) Large-artery atherosclerosis	
No	0
Yes	1
(E) Early seizure (≤7 days)	
No	0
Yes	3
(C) Cortical involvement	
No	0
Yes	2
(T) Territory of MCA	
No	0

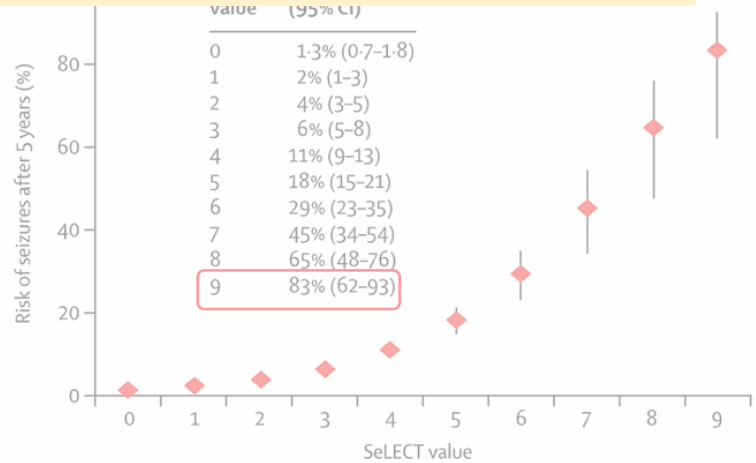


Of note, there are still limited data on the diagnostic and therapeutic effect of these models, and we are not yet using them in treatment decisions.

Further validation and examination of the clinical roles of these models are warranted.



(C) Risk of remote symptomatic seizures after 1 year



(D) Risk of remote symptomatic seizures after 5 years

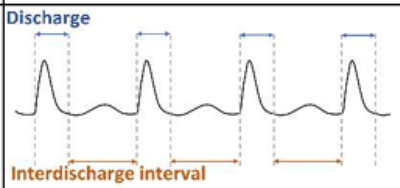
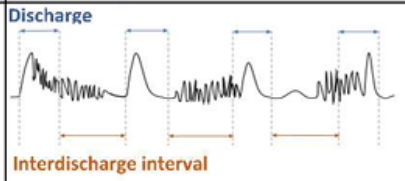
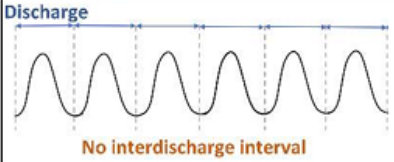
Galovic et al. *Drugs & Aging*. 2021; 38:285–299.

sTable 1: Risk factors for PSE development

Category	Variables
Ischemic stroke	
Age, sex	≥80 years[1] Younger age[2, 3] (<65 years[4]) Male[4, 5]
Genetics	*TRPM6* rs2274924 polymorphism[6] *CD40* rs1883832 polymorphism[7] *ALDH2* rs671 polymorphism[8]
Stroke lesion	Cortical involvement[3, 9-17] Middle cerebral artery lesion[13, 18] Temporal lobe[19, 20] Parietal lobe[21] Supratentorial[16, 22] Anterior circulation[5, 23] Watershed infarction[24]
Stroke characteristics	Large-artery atherosclerosis[13, 17] Sinus thrombosis[25] Hemorrhagic transformation[3, 5, 16, 22, 26, 27] Laminar necrosis[27] Scattered surviving cortical "islands"[28] Stroke recurrence[29]
Stroke severity	High NIHSS score[13, 14, 25] (NIHSS ≥11)[17] Scandinavian Stroke Scale <30[30] Large infarct (over one-half hemisphere)[10] Large stroke lesion[4, 27] (>35mm in diameter)[11] High mRS[31] (mRS >2)[16] Low Barthel Index at discharge[19] Prolonged hospital stay (>2 weeks)[1] ICU admission[1]
Small vessel diseases	Enlarged perivascular space[32] Cortical superficial siderosis[33]
Stroke treatment	Decompressive craniectomy[34] Intravenous alteplase[2, 35]
CNS comorbidities	Early seizure[3, 5, 10, 13, 15-17, 29] Seizure on stroke admission[1] Hippocampal sclerosis[36] Epileptiform abnormalities within 7 days after stroke[37, 38]

	Dementia[1, 39] Lower MMSE[31] Depression or use of antidepressants[5]
Other comorbidities	Pre-existing atrial fibrillation[1] Infection acquired during the hospital stay[19] Pneumonia on stroke admission[1] Hyperglycemia[5]
Serum biomarkers	Neuropeptide Y[40] IL-6[41] IL-1β[42]
Hemorrhagic stroke	
Age	Younger age (<65 years)[43-45]
Genetics	*APOE* ε4[46]
Stroke lesion	Cortical involvement[14, 15, 43-46]
Stroke severity	Larger hematoma volume (>10 mL)[43, 45] NIHSS (≥15)[44]
Small vessel diseases	Multiple prior lobar hemorrhages[46] Lobar microbleeds[47] Cortical superficial siderosis[33]
Stroke treatment	Surgical evacuation of hematoma[45]
CNS comorbidities	Early seizure[15, 43, 44] Pre-hemorrhage dementia[46]

EEG findings of PSE

	Morphology	Definition	Detection rate (%)	Functional decline at 6 months Crude Odds ratio [95% CI]
Interictal epileptiform discharges (IEDs)		Di- or tri-phasic waves with sharp or spiky morphology different from background activity, usually followed by an associated slow after-wave	73/245 (29.8%)	0.96 [0.49 – 1.85]
Periodic discharges (PDs)		Repetition of a relatively uniform waveform (including spike, sharp, sharp contoured, blunt) with regular intervals, lasting ≤0.5 seconds and continuing more than 6 cycles	47/245 (19.2%)	1.42 [0.69 – 2.93]
Periodic discharges with superimposed fast activity (PDs+F)		PDs plus superimposed, admixed, or associated fast activity	12/245 (5.3%)	3.20 [1.03 – 9.96]
Rhythmic delta activities (RDAs)		Repetition of a relatively uniform delta waveform without intervals, with a frequency of 0.5 to 4Hz, and continuing more than 6 cycles	43/245 (17.6%)	1.23 [0.58 – 2.65]
Intermittent delta activity		Focal irregular (excluding rhythmic waves) delta activities were intermittently observed at a focal area of the side of the stroke lesion	209/245 (85.3%)	0.52 [0.24 – 1.12]

The detection rate are based on a previous study including the first routine EEG during acute hospitalization for late seizures after stroke.

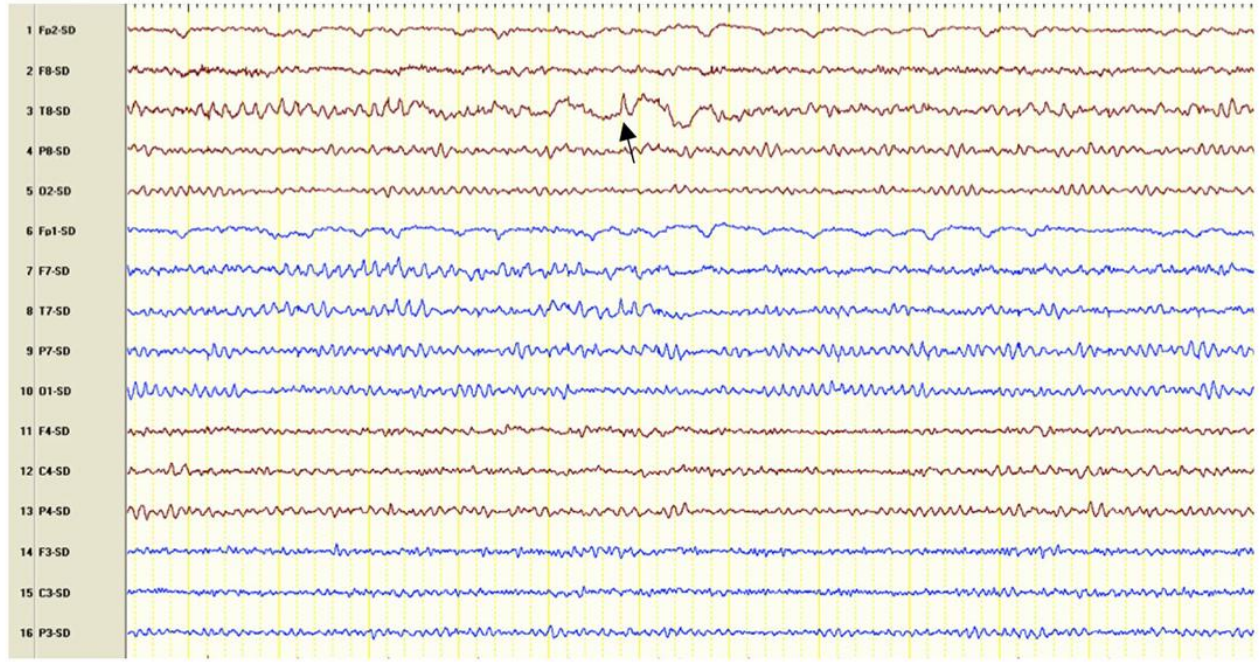
The functional decline at 6 months after discharge is defined as an increase in the modified Rankin Scale score compared with baseline.

The definitions of EEG findings are based on the American Clinical Neurophysiology Society Standardized Critical Care EEG Terminology.

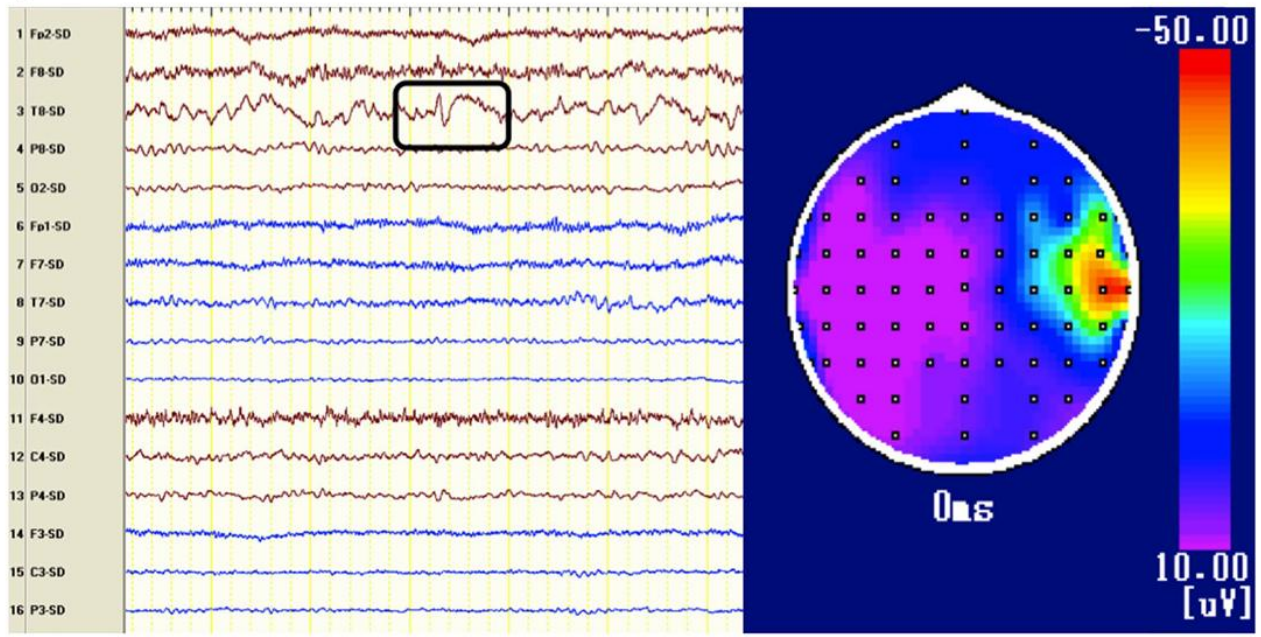
PSE: post-stroke epilepsy, CI : confidence interval

Tomotaka et al. *Neurology.* 2024; 102:e209450.

a


1 Fp2-SD
2 F8-SD
3 T8-SD
4 P8-SD
5 O2-SD
6 Fp1-SD
7 F7-SD
8 T7-SD
9 P7-SD
10 O1-SD
11 F4-SD
12 C4-SD
13 P4-SD
14 F3-SD
15 C3-SD
16 P3-SD

b


1 Fp2-SD
2 F8-SD
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5 O2-SD
6 Fp1-SD
7 F7-SD
8 T7-SD
9 P7-SD
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11 F4-SD
12 C4-SD
13 P4-SD
14 F3-SD
15 C3-SD
16 P3-SD
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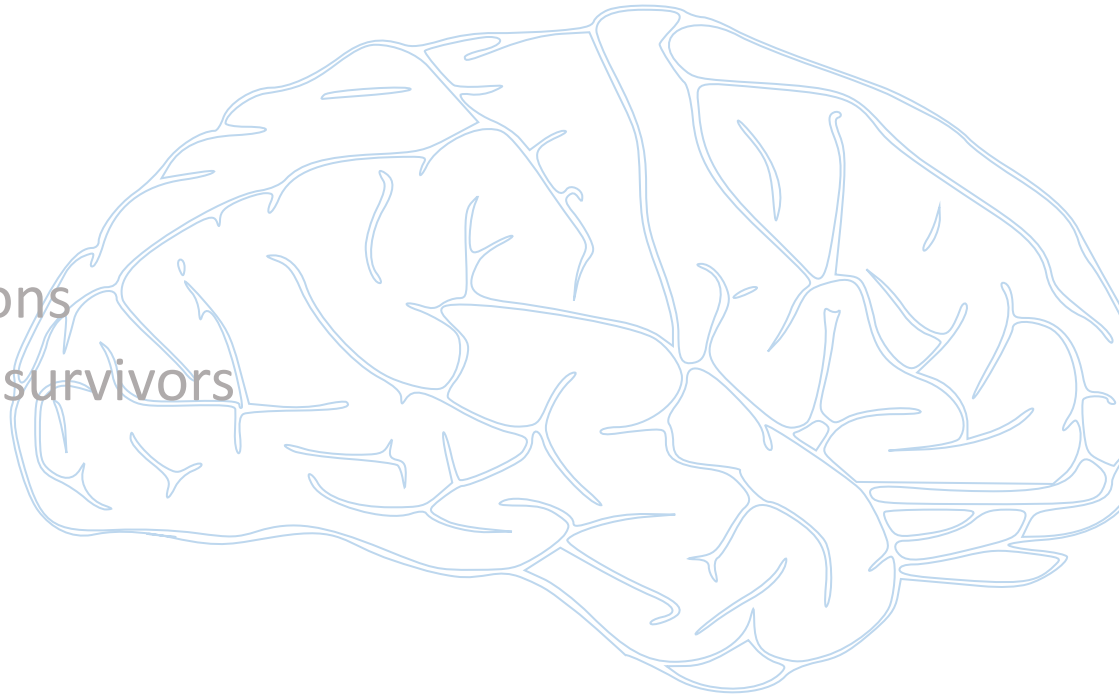
[uV]

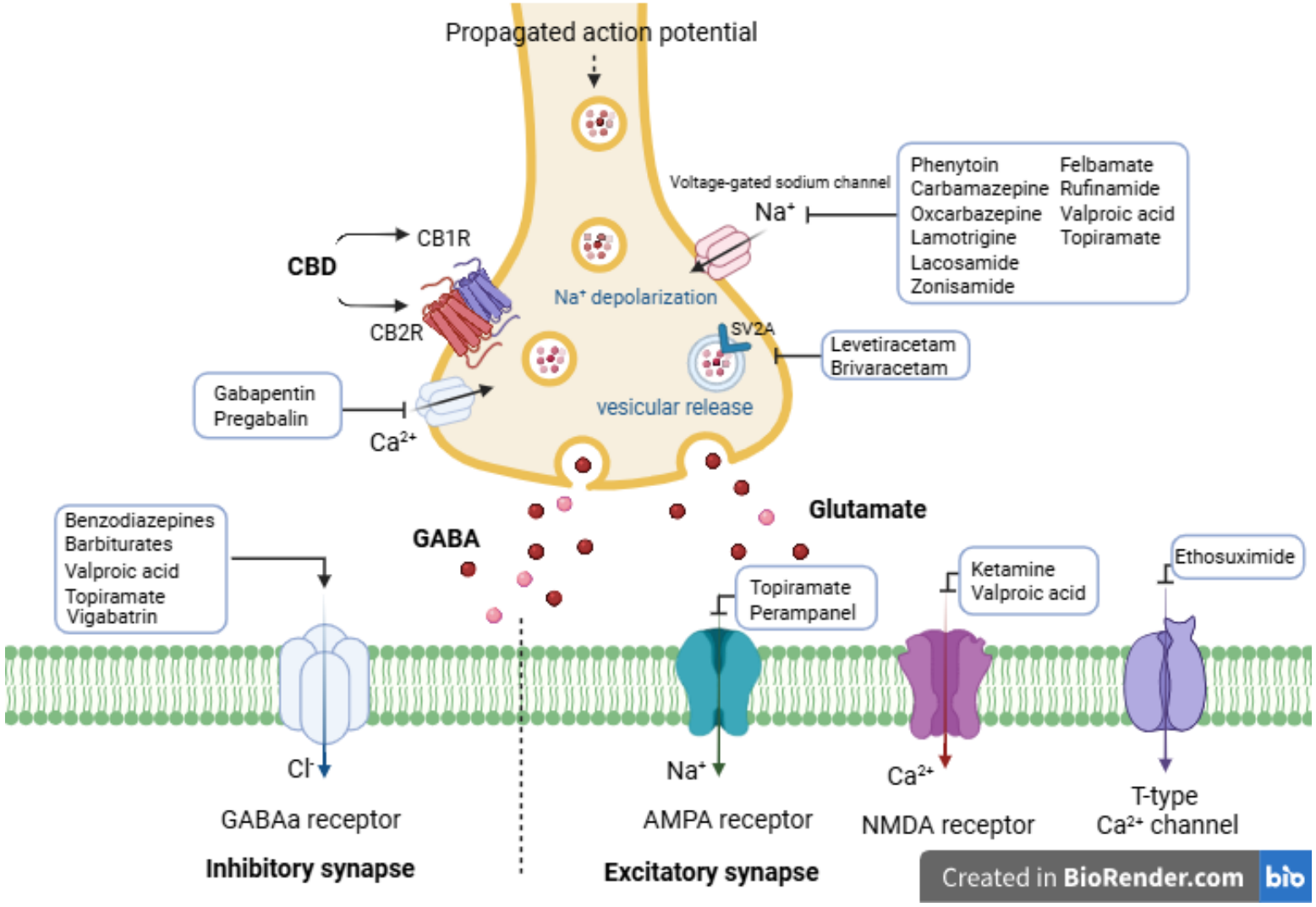
Treatment

- When to start ASM
- First-line antiepileptic drugs
  - Choices for elderly: tolerability & interactions
  - Co-morbidities & co-medications in stroke survivors
- Duration of treatment
- Discontinuation considerations



Galovic et al. *Drugs & Aging*. 2021; 38:285–299.

Mechanism of Antiepileptic drugs



by Wannisa Wongpipathpong, MD.

When to start Anti-seizure medications

- Primary prophylaxis
  - to prevent the occurrence of the first seizure after stroke
- Secondary prophylaxis
  - Antiseizure medications (ASMs) are often given as a secondary prophylactic measure to prevent subsequent seizures after stroke

Primary outcome: seizure recurrence
Secondary outcomes: cognitive impairment, adverse events, drug discontinuation rate or mortality in patients with epilepsy

Primary Prophylaxis

- Primary Prophylaxis Antiepileptogenesis trials are challenging to conduct, and evidence from randomized controlled trials (RCTs) for primary prevention is lacking
- Due to sparse reliable evidence, the European Stroke Organization guidelines suggest against general primary antiseizure medication (ASM) prophylaxis administration
- Valproic acid, diazepam, and levetiracetam have been tested for primary prevention in RCTs but failed to show efficacy or safety
- Statin use appears to prevent PSE (OR, 0.60; 95% CI, 0.42 to 0.84) and early seizures (OR, 0.36; 95% CI, 0.42 to 0.84) probably due to its anti-inflammatory and other pleiotropic effects, though this has not been confirmed

Chang RS et. al. *Cochrane Database Syst Rev*. 2022;2:CD005398.
Peter-Derex L et. al. **PEACH trial phase III.** *Lancet Neurol.* 2022;21(9):781-791.
Holtkamp M et. al. **ESO guidelines for the management of post-stroke seizures and epilepsy**. *Eur Stroke J*. 2017;2(2):103-115.

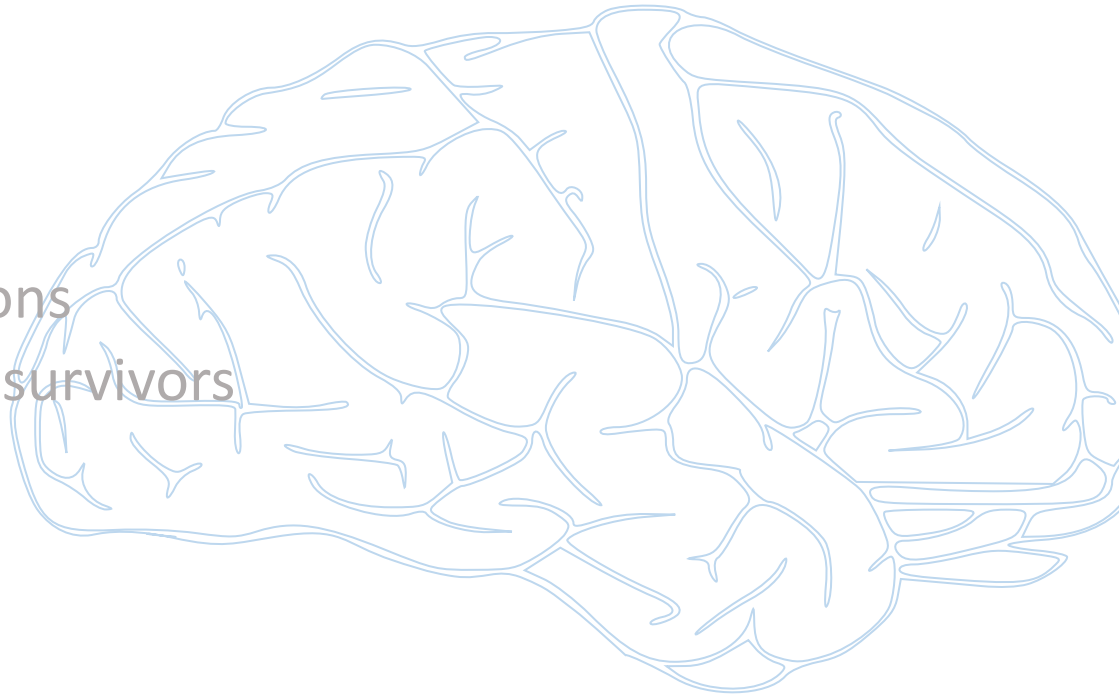
Strategies for Secondary Prophylaxis

1. patient-related factors : age, sex, comorbidities, history of drug allergy
2. seizure-related factors : focal onset, generalized onset, unknown onset
3. anti-seizure medication (ASM)-related factors : pharmacodynamics, pharmacokinetics

A pragmatic approach is to ‘start slow and aim low’.
Many patients with post-stroke epilepsy respond well to even low dose treatment.
Monotherapy is usually preferred to polytherapy.

Treatment

- When to start ASM
- First-line antiepileptic drugs
  - Choices for elderly: tolerability & interactions
  - Co-morbidities & co-medications in stroke survivors
- Duration of treatment
- Discontinuation considerations



Galovic et al. *Drugs & Aging*. 2021; 38:285–299.

RESEARCH ARTICLE

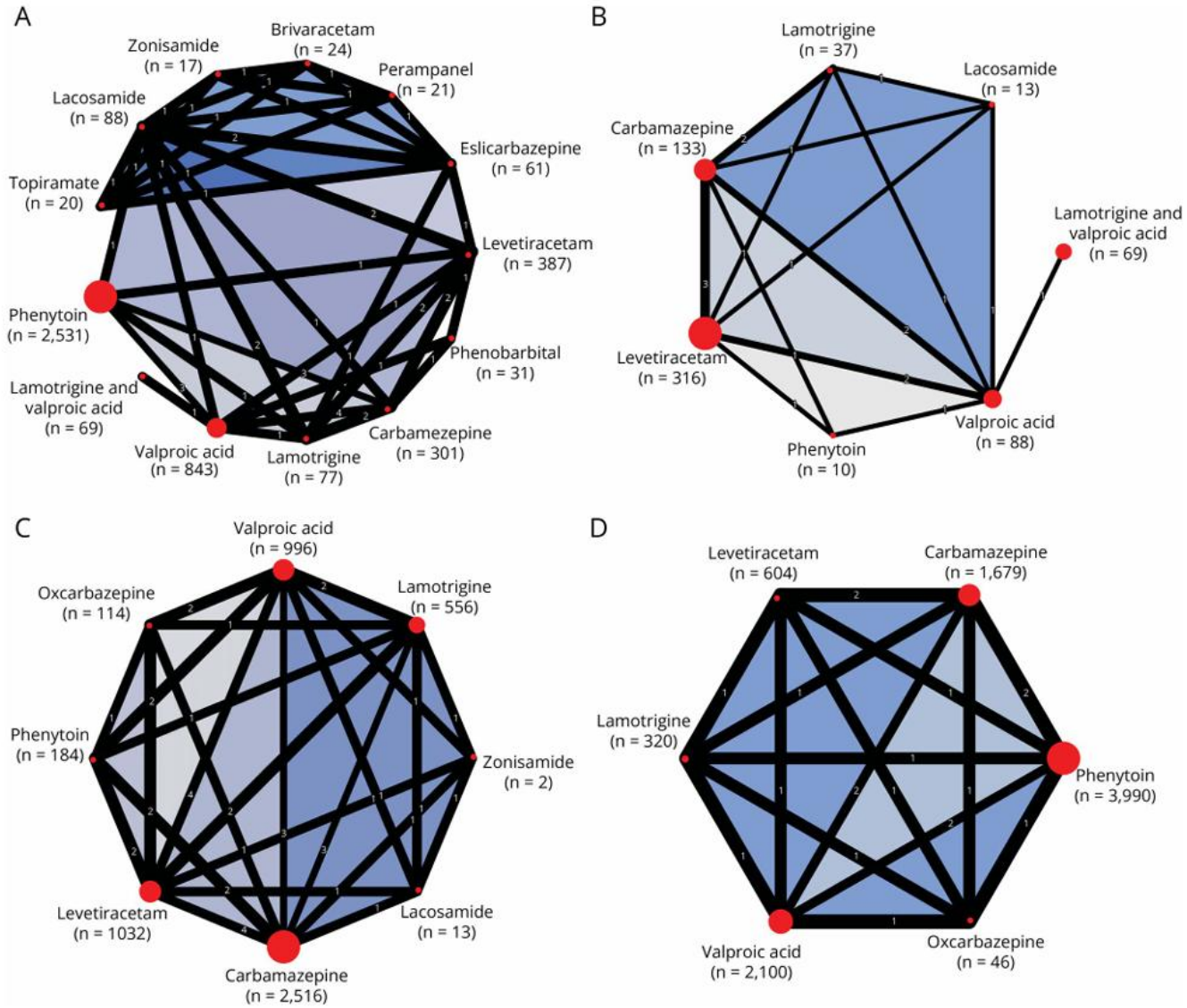
Antiseizure Medications in Poststroke Seizures

A Systematic Review and Network Meta-Analysis

Shubham Misra,[1] Selena Wang,[2,3] Terence J. Quinn,[4] Jesse Dawson,[4] Johan Zelano,[5,6] Tomotaka Tanaka,[7] James C. Grotta,[8] Erum Khan,[9] Nitya Beriwal,[10] Melissa C. Funaro,[11] Sravan Perla,[12] Priya Dev,[13] David Larsson,[5,6] Taimoor Hussain,[1,14] David S. Liebeskind,[15] Clarissa Lin Yasuda,[16] Hamada Hamid Altalib,[1,17] Hitten P. Zaveri,[1] Amr Elshahat,[1] Gazala Hitawala,[18] Ethan Y. Wang,[1] Rachel Kitagawa,[1] Abhishek Pathak,[13] Fabien Scalzo,[15,19] Masafumi Ihara,[7] Katharina S. Sunnerhagen,[5,6] Matthew R. Walters,[4] Yize Zhao,[2] Nathalie Jette,[20] Scott E. Kasner,[21] Patrick Kwan,[22] and Nishant K. Mishra[1,17]

Neurology® 2025;104:e210231. doi:10.1212/WNL.0000000000210231

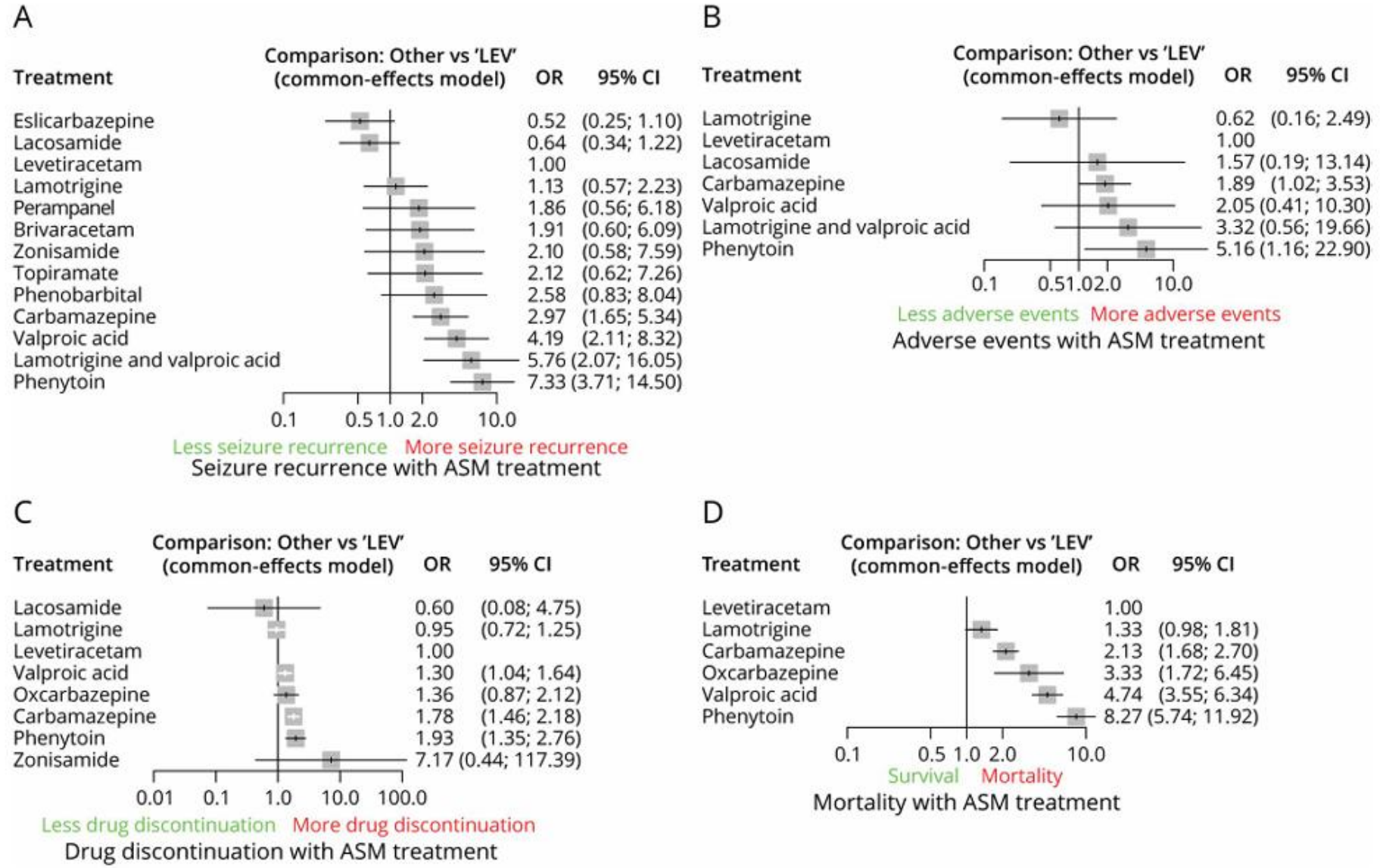
A network meta-analysis of 15 studies, including 18,676 participants with poststroke seizures, compared 13 ASMs: levetiracetam, carbamazepine, phenytoin, valproic acid, lamotrigine, lacosamide, phenobarbital, oxcarbazepine, zonisamide, eslicarbazepine, brivaracetam, perampanel, and topiramate. This suggested that lamotrigine and levetiracetam may be safe and tolerable options in this population.



The node size in red represents the total number of patients with PSS taking ASMs, and the edge thickness in black represent the total number of studies comparing ASMs in patients with PSS. ASM = antiseizure medication; PSS = poststroke seizure.

Network Diagram of Treatment Comparisons for (A) Seizure Recurrence, (B) Adverse Events, (C) Drug Discontinuation, and (D) Mortality

Figure 3 Forest Plots for the Association of Various Treatments With (A) Seizure Recurrence, (B) Adverse Events, (C) Drug Discontinuation, and (D) Mortality Compared With Levetiracetam (Reference Treatment)



ASM = antiseizure medication; LEV = levetiracetam.

Figure 4 NMA Results Sorted Based on GRADE Certainty of Evidence and Effect Estimate for the Comparisons of ASM Treatments for Seizure Recurrence, Adverse Events, Drug Discontinuation, and Mortality in Patients With PSS

Treatment	Seizure recurrence	Adverse events	Drug discontinuation	Mortality
Levetiracetam (reference)	-	-	-	-
Carbamazeine	2.97 (1.65–5.34)	1.89 (1.02–3.53)	1.78 (1.46–2.18)	2.13 (1.68–2.70)
Phenytoin	7.33 (3.71–14.50)	5.16 (1.16–22.90)	1.93 (1.35–2.76)	8.27 (5.74–11.92)
Valproic acid	4.19 (2.11–8.32)	2.05 (0.41–10.30)	1.30 (1.04–1.64)	4.74 (3.55–6.34)
Lamotrigine	1.13 (0.57–2.23)	0.16 (0.03–0.89)	0.95 (0.72–1.25)	1.33 (0.98–1.81)
Lamotrigine + valproic acid	5.76 (2.07–16.05)	3.32 (0.56–19.66)	-	-
Lacosamide	0.38 (0.06–2.48)	1.57 (0.19–13.14)	0.60 (0.08–4.75)	-
Phenobarbital	2.58 (0.83–8.04)	-	-	-
Oxcarbazepine	-	-	1.36 (0.87–2.12)	3.33 (1.72–6.45)
Zonisamide	2.10 (0.58–7.59)	-		
Eslicarbazepine	0.52 (0.25–1.10)	-		
Perampanel	1.86 (0.56–6.18)	-		
Topiramate	2.12 (0.62–7.26)	-		
Brivaracetam	1.91 (0.60–6.09)	-		

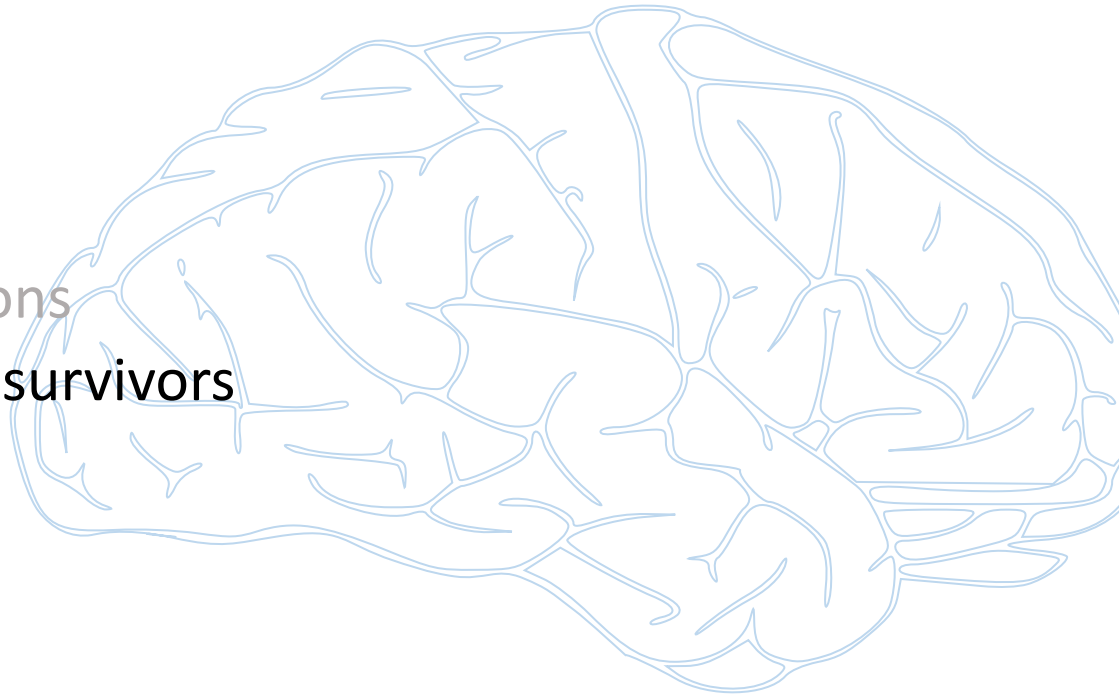
Key	High/moderate certainty evidence	Low/very low certainty evidence
Among the best	Less harmful than reference and some alternatives	Might be less harmful than reference and some alternatives
Among the better	No more harmful than reference but less harmful than some alternatives	Might be no more harmful than reference but less harmful than some alternatives
Indifferent	No more harmful than reference	Might be no more harmful than reference
Intermediate	More harmful than reference but no worse than any alternatives	Might be more harmful than reference but no worse than any alternatives
Among the worst	More harmful than reference and some alternatives	Might be more harmful than reference and some alternatives

Although first-generation ASMs (eg, phenytoin, valproate, and carbamazepine) are the most widely prescribed, newer-generation ASMs have better efficacy and adverse effect profiles. Despite their potential effectiveness, some of the newest agents (eg, perampanel and eslicarbazepine) have not been extensively validated or evaluated.

ASM = antiseizure medication; NMA = network meta-analysis; PSS = poststroke seizure.

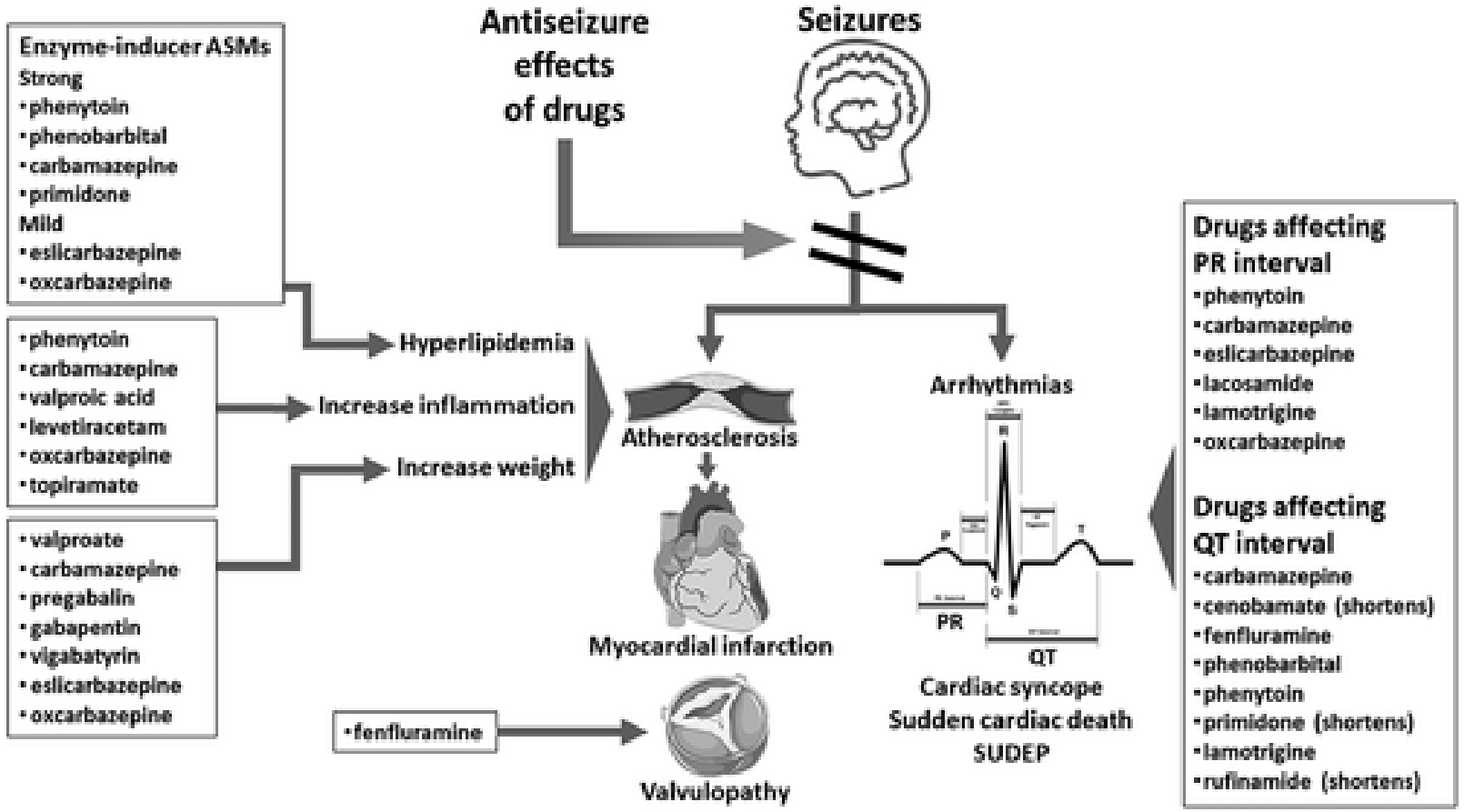
Treatment

- When to start ASM
- First-line antiepileptic drugs
  - Choices for elderly: tolerability & interactions
  - Co-morbidities & co-medications in stroke survivors
- Duration of treatment
- Discontinuation considerations



Galovic et al. *Drugs & Aging*. 2021; 38:285–299.

Atherosclerotic risk and cardiovascular disease in stroke survivor



https://doi.org/10.1080/14740338.2022.2023128

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.

Drug-drug interaction (DDI)

Enzyme inducers

*Older generation ASMs : PHT, PB, CBZ

- Decrease level of CCB
  - nondihydropyridine type : nifedipine and nimodipine
  - dihydropyridine type : diltiazem and verapamil
    (verapamil and diltiazem inhibits carbamazepine metabolism)
- Decrease level of beta-blocker
- Decrease level of warfarin and NOACs
- Phenytoin → decrease amiodarone level (CYP induction)
  digoxin level (upregulation of P-gp)

* Second- and third-generation ASMs

- Perampanel same as first-generation ASM (potent CYP3A4 inducer)
- LEV and LTG are preferred ASMs with minimal DDIs, but DDIs exist

ESC European Society of Cardiology

Europace (2021) **23**, 1612–1676
doi:10.1093/europace/euab065

POSITION PAPER
EHRA Practical Guide

2021 European Heart Rhythm Association Practical Guide on the Use of Non-Vitamin K Antagonist Oral Anticoagulants in Patients with Atrial Fibrillation

Jan Steffel[1]*, Ronan Collins[2], Matthias Antz[3], Pieter Cornu[4], Lien Desteghe[5,6], Karl Georg Haeusler[7], Jonas Oldgren[8], Holger Reinecke[9], Vanessa Roldan-Schilling[10], Nigel Rowell[11], Peter Sinnaeve[12], Thomas Vanassche[12], Tatjana Potpara[13], A. John Camm[14], and Hein Heidbüchel[5,6]

Table 7 **Anticipated effects of common antiepileptic drugs on non-vitamin K antagonist oral anticoagulants plasma levels**

	Via[426, 539-541]	Dabigatran etexilate	Apixaban	Edoxaban	Rivaroxaban
P-gp substrate		Yes	Yes	Yes	Yes
CYP3A4 substrate		No	Yes (≈25%)	No (<4%)	Yes (≈18%)
Drug					
Brivaracetam	–	No relevant interaction known/assumed			
Carbamazepine	Strong CYP3A4/P-gp induction; CYP3A4 competition	-29% [542]	-50% (SmPC)	SmPC	SmPC
Ethosuximide	CYP3A4 competition	No relevant interaction known/assumed			
Gabapentin	–	No relevant interaction known/assumed			
Lacosamide	–	No relevant interaction known/assumed			
Lamotrigine	P-gp competition	No relevant interaction known/assumed			
Levetiracetam	P-gp induction; P-gp competition				
Oxcarbazepine	CYP3A4 induction; P-gp competition				
Phenobarbital	Strong CYP3A4/possible P-gp induction		SmPC	SmPC	SmPC
Phenytoin	Strong CYP3A4/P-gp induction; P-gp competition	SmPC [543]	SmPC	SmPC	SmPC
Pregabalin	–	No relevant interaction known/assumed			
Topiramate	CYP3A4 induction; CYP3A4 competition				
Valproic acid	CYP3A4/P-gp induction/inhibition				Ref 544
Zonisamide	CYP3A4 competition; weak P-gp inhibition	No relevant interaction known/assumed (SmPC)			

Colour coding is based on the respective NOAC SmPC, drug interaction databases, or expert opinion.[426] The hatched colour coding indicates no clinical or PK data available. Some of the colour codes will likely require adaptation as more data become available over time.

No relevant drug-drug interaction anticipated

Caution required. Especially in case of polypharmacy or in the presence of ≥ light blue interactions due to reduced DOAC plasma levels

Contraindicated due to reduced DOAC plasma levels

ESC European Society of Cardiology

European Heart Journal (2019) **40**, 3800–3801
doi:10.1093/eurheartj/ehz657

DISCUSSION FORUM

Levetiracetam and non-vitamin K antagonist oral anticoagulants in patients with atrial fibrillation and epilepsy: a reasonable combination

Tim J. von Oertzen [1]*, Eugen Trinka [2], and Natan M. Bornstein[3]

[1]Department of Neurology 1, Kepler Universitätsklinikum, Wagner-JureggWeg 15, 4020 Linz, Austria, and European Academy of Neurology (EAN), Scientific Panel Epilepsy; [2]Department of Neurology, Christian Doppler Klinik, University Hospital Paracelsus Medical University, Ignaz-Harrer-Straße 79, 5020 Salzburg, Austria, International League Against Epilepsy Europe (ILAE-EUROPE) and EAN Scientific Panel Epilepsy; and [3]Shaarei Zedek Medical Center, 12 Shmuel Bait St., Jerusalem 9103102, Israel and EAN Scientific Panel Stroke

- There is no evidence for levetiracetam to cause P-gp mediated drug–drug interaction with NOACs in humans.
- In reply, the guidance authors argued that caution needs to be applied in order to have effective NOAC therapy.

(1) The rate of post-stroke epilepsy (PSE) is expected in 8% of stroke patients after 5 years. Predictors include severity of stroke, cortical involvement, and territory of middle cerebral artery involvement,[4] indicating a high proportion of patients with AF as stroke aetiology and the need of life-long oral anticoagulant and antiepileptic therapy.

(2) So far, there are no clinically relevant drug–drug interactions known with levetiracetam. Additional characteristics such as linear pharmacokinetics, renal clearance, and little risk for cognitive impairment are particular useful features for AED treatment with levetiracetam in the elderly with multimorbidity and polypharmacotherapy.

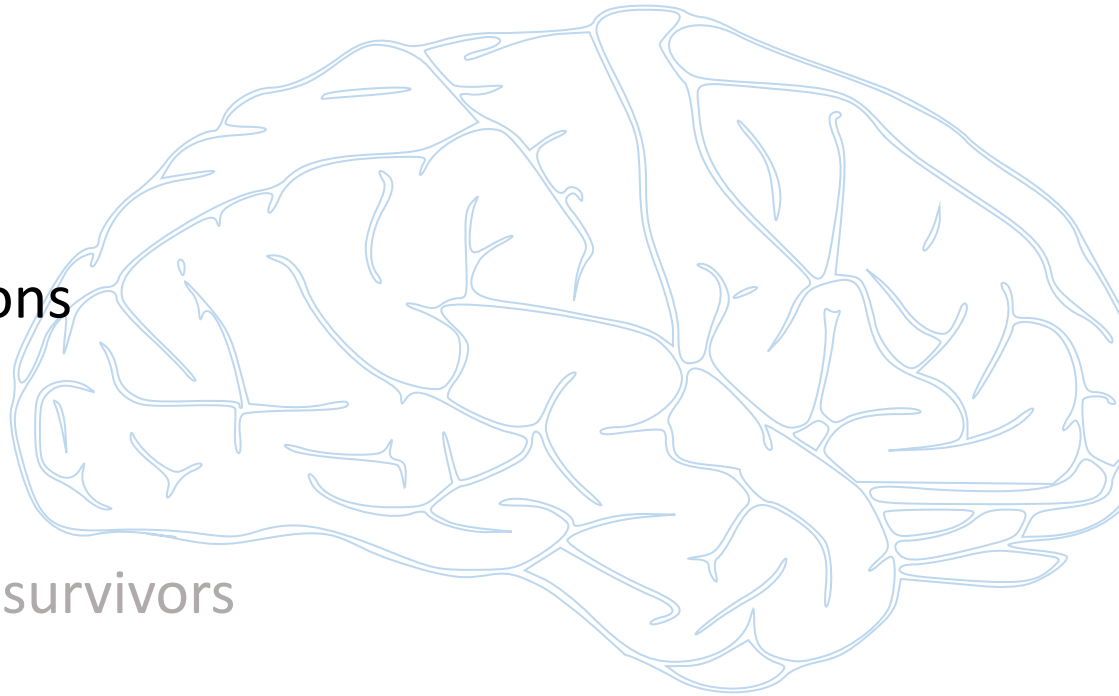
(3) Levetiracetam was shown to be superior to extended release carbamazepine in a randomized controlled trial in the elderly, mostly suffering from PSE. Superiority in AED trials is rarely reached, so this result is highly respected.[5]

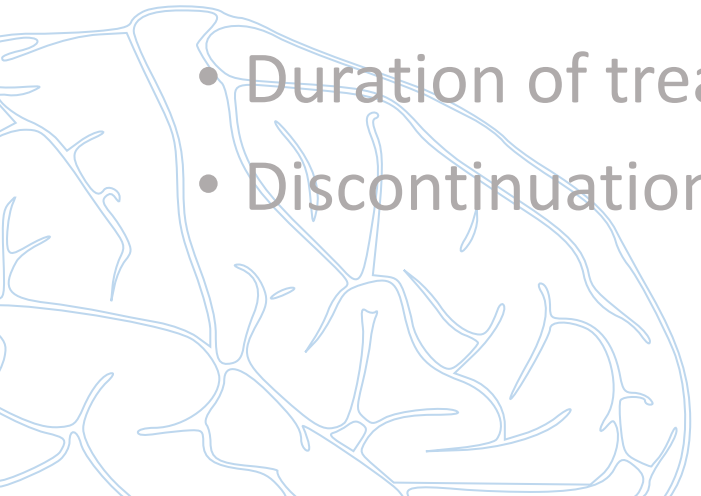
(4) PSE is a serious condition with increased mortality and reduced functional outcome. Withholding or switching a well-established therapy with levetiracetam according to the advice given in the guidance, puts patients on significant risk of break through seizures and status epilepticus including an additional risk for injuries including intracranial haemorrhage under NOAC therapy.

Therapeutic drug monitoring for levetiracetam and NOAC levels should be sufficient to indicate if subtherapeutic NOAC therapy might increase risk for recurrent stroke of embolic cardiac etiology.

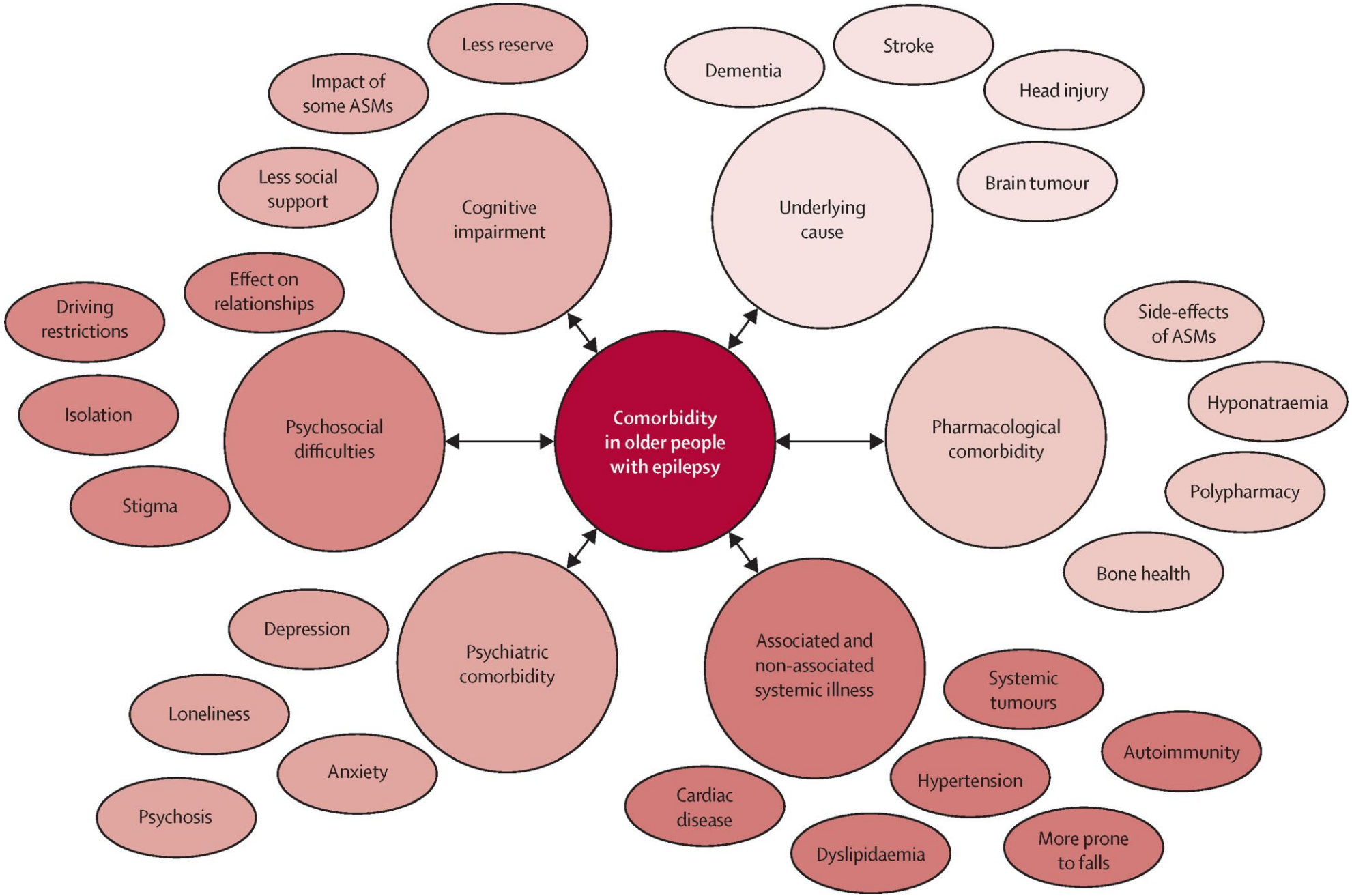
Treatment

- When to start ASM
- First-line antiepileptic drugs
  - Choices for elderly: tolerability & interactions
    - Age-related pharmacokinetics & comorbidities
    - Drug-drug interactions (polypharmacy)
    - Cognitive side effects & fall risk
  - Co-morbidities & co-medications in stroke survivors
- Duration of treatment
- Discontinuation considerations





Galovic et al. *Drugs & Aging*. 2021; 38:285–299.


Comorbidity in older people with epilepsy
Cognitive impairment
Less reserve
Impact of some ASMs
Less social support
Underlying cause
Dementia
Stroke
Head injury
Brain tumour
Psychosocial difficulties
Effect on relationships
Driving restrictions
Isolation
Stigma
Pharmacological comorbidity
Side-effects of ASMs
Hyponatraemia
Polypharmacy
Bone health
Psychiatric comorbidity
Depression
Loneliness
Anxiety
Psychosis
Associated and non-associated systemic illness
Systemic tumours
Autoimmunity
Hypertension
Cardiac disease
Dyslipidaemia
More prone to falls

Cautions of adverse effects of ASM in elderly

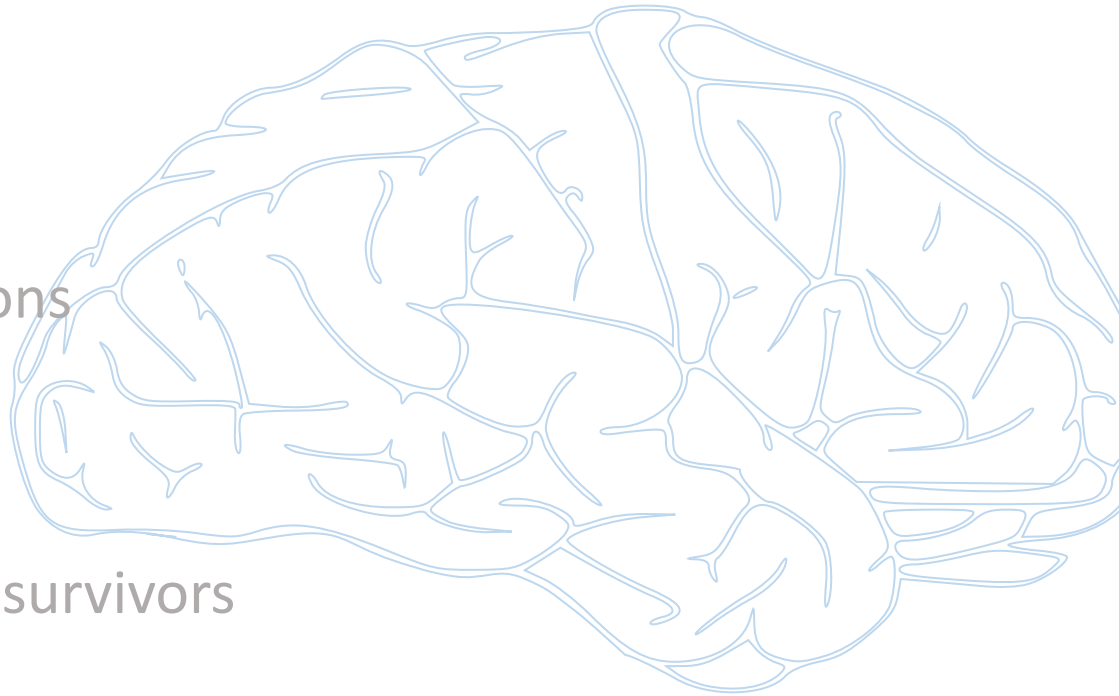
ASM	Special precaution
Benzodiazepines	Somnolence, aggression, irritability, cognitive dysfunction, tolerance, dependence
Phenobarbital	Somnolence, dizziness, nausea, cognitive dysfunction Enzyme inducer
Phenytoin	Hypotension, nausea, dizziness, ataxia, nystagmus, osteoporosis Enzyme inducer
Carbamazepine	Hyponatremia, dizziness, blurred vision Enzyme inducer
Valproate	Nausea, dizziness, tremor, somnolence, thrombocytopenia
Topiramate	Cognitive dysfunction at higher doses, dizziness

Common and adverse effects of commonly used newer antiseizure medication

ASD	Systemic	Neurologic	Rare idiosyncratic reactions
Brivaracetam	Nausea, vomiting, constipation, and fatigue	Headache, somnolence, dizziness, abnormal coordination, nystagmus, and mood changes	
Eslicarbazepine	Nausea, vomiting, diarrhea, hyponatremia, and rash	Dizziness, drowsiness, headache, somnolence, diplopia, ataxia, blurred vision, and tremor	
Felbamate	Nausea, vomiting, anorexia, and weight loss	Insomnia, dizziness, headache, and ataxia	Aplastic anemia and severe hepatitis/hepatic failure
Fosphenytoin	Fever, injection-site reaction and pain, infection, chills, face edema, hypertension, constipation, hypokalemia, myasthenia, pneumonia, and rash	Increased reflexes, speech disorder, dysarthria, intracranial hypertension, thinking abnormal, and aggression	Lower incidence of purple glove syndrome than intravenous phenytoin
Gabapentin	Infrequent	Somnolence, dizziness, ataxia, headache, tremor, and fatigue	
Lacosamide	Nausea, vomiting, and increased cardiac conduction (PR interval)	Dizziness, ataxia, diplopia, and headache	
Lamotrigine	Nausea, rash, and cardiac arrhythmias	Dizziness, tremor, and diplopia	Steven–Johnson syndrome
Levetiracetam	Fatigue, infection, anemia, and leukopenia	Somnolence, dizziness, agitation, anxiety, irritability, depression, and psychosis	
Oxcarbazepine	Nausea, rash, and hyponatremia (more common)	Somnolence, headache, dizziness, vertigo, ataxia, and diplopia	
Perampanel	Weight gain, fatigue, and nausea	Dizziness, somnolence, irritability, gait disturbance, falls (with high dose), aggression, and mood alteration	
Pregabalin	Weight gain, peripheral edema, and dry mouth	Somnolence, dizziness, ataxia, headache, and tremor	
Tiagabine	Abdominal pain, nausea, and lack of energy	Dizziness, difficulty concentrating, somnolence, nervousness, tremor, and language problems	
Topiramate	Anorexia, weight loss, paresthesia, and fatigue	Nervousness, psychomotor slowing, language problems, depression, anxiety, mood problems, and tremor	Acute glaucoma (may require prompt drug withdrawal)
Vigabatrin	Fatigue	Somnolence, headache, dizziness, agitation, confusion, and psychosis	Irreversible bilateral concentric visual field defect (vision loss)
Zonisamide	Weight loss, nausea, and anorexia	Somnolence, dizziness, ataxia, confusion, headache, depression, and psychosis	Potentially serious skin rashes

Treatment

- When to start ASM
- First-line antiepileptic drugs
  - Choices for elderly: tolerability & interactions
    - Age-related pharmacokinetics & comorbidities
    - Drug-drug interactions (polypharmacy)
    - Cognitive side effects & fall risk
  - Co-morbidities & co-medications in stroke survivors
- Duration of treatment
- Discontinuation considerations



Galovic et al. *Drugs & Aging*. 2021; 38:285–299.

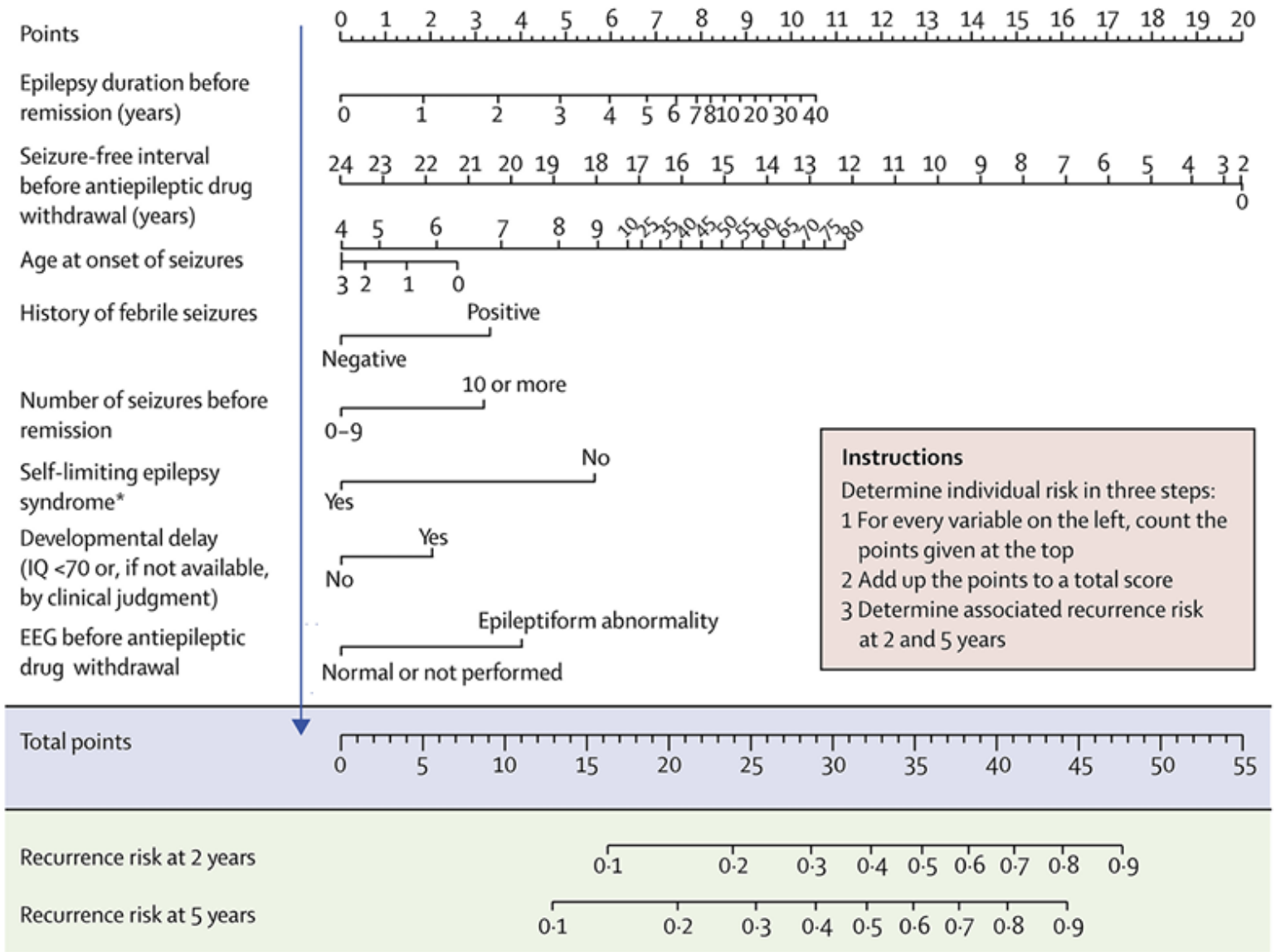
Withdrawal of Antiseizure Medication

- Withdrawal after at least 2 years of seizure freedom may reduce the risk of relapses compared with earlier withdrawal

- Given that more than two-thirds of individuals with post-stroke epilepsy achieve seizure freedom with one ASM, which is similar to other epilepsy etiologies, some of these individuals may benefit from medication withdrawal

Silverman *et al.* 2002; Bryndziar *et al.* 2015.

Prediction of seizure recurrence after antiseizure medication withdrawal. Nomogram to predict seizure recurrence risk after 2 or 5 years following antiseizure medication withdrawal. The nomogram is not specific to post-stroke epilepsy. Reproduced from Lamberink et al. [133] with permission



Prevention from stroke-related epilepsy

RESEARCH ARTICLE

Epilepsia®

Vascular risk factors as predictors of epilepsy in older age: The Framingham Heart Study

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We studied the role of modifiable vascular risk factors in predicting subsequent epilepsy among participants ages 45 or older in the Framingham Heart Study (FHS), a longitudinal, community-based study.

Stefanidou M, Himali JJ, Devinsky O, Romero JR, Ikram MA, Beiser AS, et al. Vascular risk factors as predictors of epilepsy in older age: The Framingham Heart Study. *Epilepsia*. 2022; 63: 237–243.

Abstract

Objective: Stroke is the most common cause of epilepsy in older age. Subclinical cerebrovascular disease is believed to underlie some of the 30%–50% of late-onset epilepsy without a known cause (Li et al. *Epilepsia*. 1997;38:1216; Cleary et al. *Lancet*. 2004;363:1184). We studied the role of modifiable vascular risk factors in predicting subsequent epilepsy among participants ages 45 or older in the Framingham Heart Study (FHS), a longitudinal, community-based study.

Methods: Participants of the Offspring Cohort who attended FHS exam 5 (1991–1995) were included who were at least 45-years-old at that time, had available vascular risk factor data, and epilepsy follow-up (n = 2986, mean age 58, 48% male). Adjudication of epilepsy cases included review of medical charts to exclude seizure mimics and acute symptomatic seizures. The vascular risk factors studied included hypertension, diabetes mellitus, smoking, and hyperlipidemia. The role of the Framingham Stroke Risk Profile score was also investigated. Cox proportional hazards regression models were used for the analyses.

Results: Fifty-five incident epilepsy cases were identified during a mean of 19 years of follow-up. Hypertension was associated with a near 2-fold risk (hazard ratio [HR]: 1.93, 95% confidence interval [CI]: 1.10–3.37, p = .022) of developing epilepsy, even after adjustment for prevalent and interim stroke. In secondary analysis, excluding patients with normal blood pressure who were receiving anti-HTN (anti-hypertensive) treatment (n = 2613, 50 incident epilepsy cases) the association was (HR: 2.44, 95% CI: 1.36–4.35, p = .003).

Significance: Our results offer further evidence that hypertension, a potentially modifiable and highly prevalent vascular risk factor in the general population, increases 2- to 2.5-fold the risk of developing late-onset epilepsy.

KEYWORDS

diabetes, elderly, epilepsy, hypertension, smoking, vascular risk factors

Key Points

- Cohort study participants with hypertension had a 2-fold risk of developing epilepsy over a 19-year follow-up.
- In sensitivity analysis, participants with uncontrolled hypertension carried an even higher risk of subsequent epilepsy.
- In this Caucasian population, presence of diabetes, hyperlipidemia, smoking, and higher Framingham Stroke Risk Profile score did not increase the risk of incident epilepsy.

Finally, in a secondary analysis looking at blood pressure as a continuous, rather than dichotomized, variable

we found that for every 10 mmHg change in systolic blood pressure there is a 17% increased hazard of subsequent epilepsy after adjusting for age and sex (HR: 1.17, 95%CI: 1.02-1.33, p = 0.02)

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.

Comparative summary of study BIA 2093-213 and other antiepileptic studies of ASMs following stroke

ASM(s) (trial name)	Clinical trial identifier	Sponsor/ centre	Study design	Primary endpoint (timepoint)	Timing of treatment initiation after stroke	Treatment duration	Duration of follow-up	Total number of patients planned (total number recruited [if completed])	Status and key results (if completed)
Eslicarbazepine acetate (Study BIA-2093-213)	EudraCT 2018-002747	BIAL – Portela & C[a], S.A.	Phase II, multicentre, placebo-controlled RCT	Failure rate (6 months)	Within 120 h	30 days	Up to 18 months	200 (125)	Ongoing
Valproic acid[41]	ClinicalTrials.gov NCT01115959	Faculty of Medicine, Tel Aviv University, Tel Aviv, Israel	Phase IV, single-centre, placebo-controlled RCT	Seizure rate (12 months)	At 2 (+2) h from intracerebral haemorrhage[a]	1 month	12 months	84 (72)	• Completed • No difference between valproic acid and placebo in risk of post-stroke seizures (risk ratio, 0.88) or death (risk ratio, 1.20)
Levetiracetam[28] (ETLAS)	–	University Hospital Maastricht, Maastricht, The Netherlands	Multicentre, placebo-controlled RCT	US rate (12 months)	48 h to 7 days	12 weeks (maintenance)	12 months	400 (16)	• Completed • Too few participants recruited to draw conclusions
Diazepam[42, 43] (EGASIS)	–	University Hospital Maastricht, Maastricht, The Netherlands	Multicentre, placebo-controlled RCT	Seizure occurrence[b] (3 months)	≤12 h[c]	3 days	3 months	(784)[d]	• Completed • No statistically significant difference in seizure occurrence between patients treated with diazepam versus placebo (risk ratio, 0.47) • No statistically significant difference in mortality between patients treated

									with diazepam versus placebo at 2 weeks (risk ratio, 0.84) and 3 months (risk ratio, 0.95) • Primary prophylaxis with diazepam was associated with a reduced risk of post-stroke seizures in patients with anterior circulation cortical infarcts (risk ratio, 0.21)
Perampanel[44] (PEPSTEP)	ClinTrial Refer ACTRN12618001984280	IIS supported by Eisai	Phase II, multicentre, placebo-controlled RCT	Seizure freedom (12 months)	Within 7 days	16 weeks (4 weeks titration; 12 weeks maintenance)	12 months	Up to 328	Open
Perampanel Levetiracetam	ClinicalTrials.gov NCT04858841	National Cheng Kung University, Taiwan	Randomised, double-blind case-control study	US rate (not available)	Not available	Not available	Not available	180	Recruiting

[a]Time to start of dosing after randomisation was 14±4 h in the valproic acid group and 16±5 h in the placebo group; [b]Occurrence of seizures was registered prospectively as one of the prespecified secondary outcomes (primary endpoint was independence [modified Rankin score <3] at 3 months; [c]Preferably within 3 h but at most within 12 h; [d]This was an exploratory antiepileptogenesis substudy of the EGASIS Trial, for which a planned sample size was not prespecified; 784 patients were included in the substudy (diazepam, n=389; placebo, n=395).

ASM, antiseizure medication; IIS, investigator-initiated study; RCT, randomised controlled trial; US, unprovoked seizure.

Take home messages

- No validated biomarkers or proven drugs for primary prevention of epilepsy (ie, those that block epileptogenic pathways) are available
- Long-term prognosis is of utmost importance, especially in young patients who usually still have a life expectancy of decades ahead
- The choice of an ideal antiseizure medication should not only rely on efficacy but also consider adverse effects, altered pharmacodynamics in older adults, and the influence on the underlying vascular co-morbidity
- Drug–drug interactions, particularly those between antiseizure medications and anticoagulants or antiplatelets, also influence treatment decisions

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Thank you for your attention

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